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New hypotheses for the health-protective mechanisms of whole-grain cereals: what is beyond fibre?

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Epidemiological studies have clearly shown that whole-grain cereals can protect against obesity, diabetes, CVD and cancers. The specific effects of food structure (increased satiety, reduced transit time and glycaemic response), fibre (improved faecal bulking and satiety, viscosity and SCFA production, and/or reduced glycaemic response) and Mg (better glycaemic homeostasis through increased insulin secretion), together with the antioxidant and anti-carcinogenic properties of numerous bioactive compounds, especially those in the bran and germ (minerals, trace elements, vitamins, carotenoids, polyphenols and alkylresorcinols), are today well-recognised mechanisms in this protection. Recent findings, the exhaustive listing of bioactive compounds found in whole-grain wheat, their content in whole-grain, bran and germ fractions and their estimated bioavailability, have led to new hypotheses. The involvement of polyphenols in cell signalling and gene regulation, and of sulfur compounds, lignin and phytic acid should be considered in antioxidant protection. Whole-grain wheat is also a rich source of methyl donors and lipotropes (methionine, betaine, choline, inositol and folates) that may be involved in cardiovascular and/or hepatic protection, lipid metabolism and DNA methylation. Potential protective effects of bound phenolic acids within the colon, of the B-complex vitamins on the nervous system and mental health, of oligosaccharides as prebiotics, of compounds associated with skeleton health, and of other compounds such as α-linolenic acid, policosanol, melatonin, phytosterols and *para*-aminobenzoic acid also deserve to be studied in more depth. Finally, benefits of nutrigenomics to study complex physiological effects of the 'whole-grain package', and the most promising ways for improving the nutritional quality of cereal products are discussed.

Whole-grain wheat: Bioactive compounds: Physiological mechanisms: Health

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Introduction

There is growing evidence that whole-grain cereal products protect against the development of chronic diseases. The most important of these in terms of public health are obesity[1,2], the metabolic syndrome[3,4], type 2 diabetes[5,6], CVD[7] and cancers[8–12]. Whole-grain cereal consumption has also been shown to be protective against mortality, as was shown with inflammation-related death (i.e. non-cardiovascular and non-cancer inflammatory diseases such as, for example, respiratory system diseases)[13] and with cancer and CVD[4,14,15]. These conclusions are supported by the effects of consuming refined cereal products (bread, pasta and rice), as these have been associated with an increased risk of digestive tract, pharynx, larynx and thyroid cancers in northern Italians[16]. However, an association between a lower risk of developing a chronic disease and a high whole-grain cereal consumption does not mean a direct causal relationship and provides no information about the physiological mechanisms involved.

These metabolic diseases are related to our daily lifestyle, notably an unbalanced energy-rich diet lacking fibre and protective bioactive compounds such as micronutrients and phytochemicals. Today, it is agreed to advance that this is the synergistic action of the compounds, mainly contained in the bran and germ fractions of cereals, which is protective[17,18]. Some specific mechanisms are today well recognised. For example, food structure influences satiety and the slow release of sugars recommended for type 2 diabetes. Dietary fibre improves gut health, and the antioxidant and anti-inflammatory properties of most phytochemicals can help

Abbreviations: AACC, American Association of Cereal Chemists; DW, dry weight; FRAP, ferric-reducing ability of plasma; GI, glycaemic index; GSH, reduced glutathione; GSSG, oxidised glutathione; RS, resistant starch; USDA, US Department of Agriculture.

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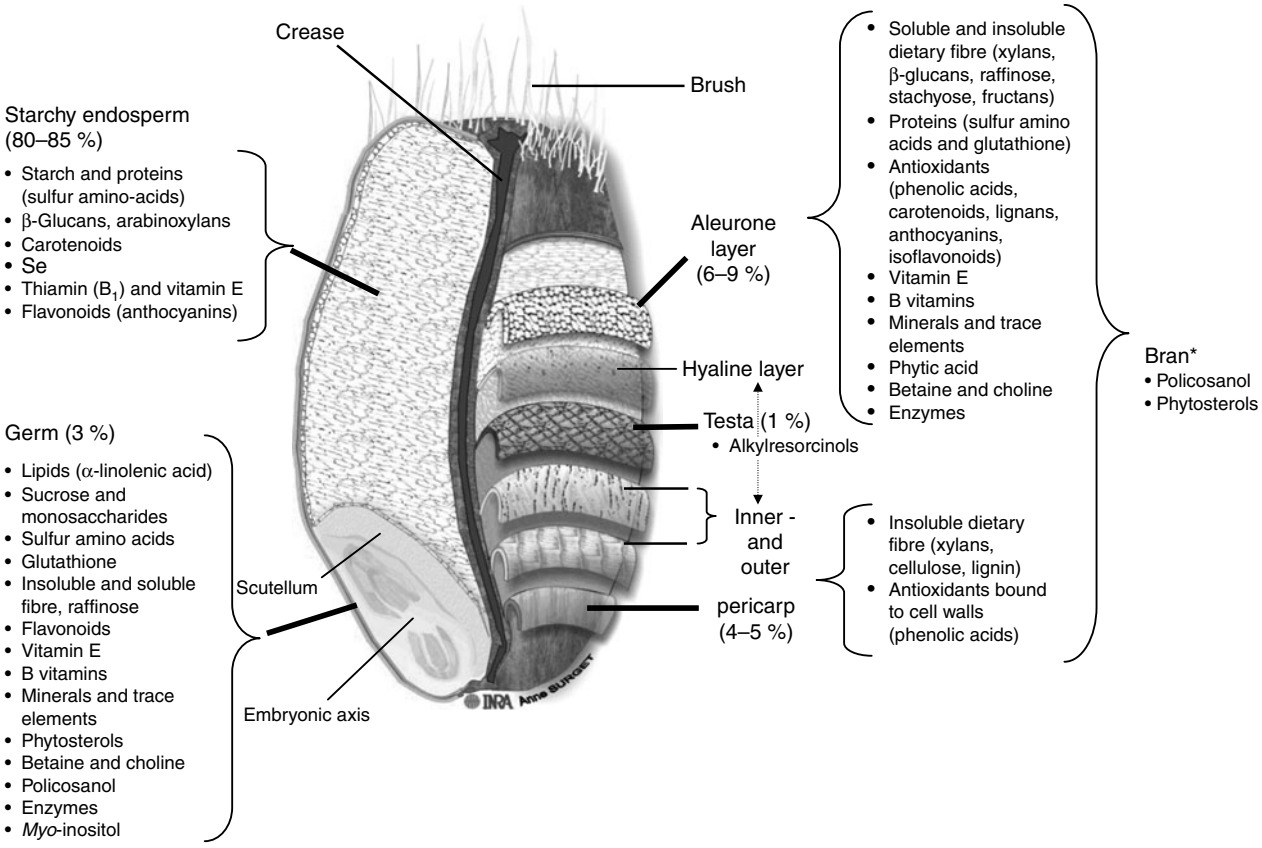

Fig. 1. The three wheat fraction (bran, germ and endosperm) with their main bioactive compounds as obtained from Tables 1 and 2. Whole-grain wheat has an heterogeneous struture with bioactive compounds unevenly distributed within its different parts (with permission from Surget & Barron for original image[476], and adapted from the brochure 'Progress in HEALTHGRAIN 2008', HealthGrain Project, European Community's Sixth Framework Programme, FOOD-CT-2005-514008, 2005–2010). * No published data on the precise locations of policosanol and phytosterols in a specific layer of the wheat bran fraction.

prevent cancer and CVD. However, the precise physiological mechanisms involved are far from being elucidated.

The main whole-grain cereals consumed worldwide are wheat, rice and maize, followed by oats, rye, barley, triticale, millet and sorghum. Whole-grain wheat, which is the focus of the present review, is composed of 10–14 % bran, 2·5–3·0 % germ and 80–85 % endosperm, depending on the intensity of the milling process. The bioactive compounds are unevenly distributed within these parts (Fig. 1), and this distribution also varies according to the type of cereal considered. Whole-grain cereals are a rich source of fibre and bioactive compounds. For example, whole-grain wheat contains about 13 % dietary fibre and at least 2 % bioactive compounds other than fibre (Table 1), which accounts for at least 15 % of the whole grain. In the bran and germ fractions, still higher proportions are reached: about 45 and 18 % of dietary fibre, and about 7 % and at least 6 % of bioactive compounds, respectively; which represents about 52 % and at least 24 % of these fractions. These proportions obviously depend on the cereal type. It is therefore easy to understand that refined cereal products that lack the bran and germ fractions have lost most of their protective compounds. For example, refining whole-grain wheat may lead to the loss of about 58 % of fibre, 83 % of Mg, 79 % of Zn, 92 % of Se, 70 % of nicotinic acid, 61 % of folates and 79 % of vitamin E[19].

However, the exact nature of the positive physiological effects exerted by whole-grain cereal products remains unresolved because of the huge number of phytochemicals and biological effects involved (Tables 2 and 3). The most significant of them in wheat, besides fibre, are *n*-3 fatty acids, sulfur amino acids, oligosaccharides (stachyose, raffinose and fructans), lignin, minerals, trace elements, vitamins B and E, carotenoids, polyphenols (especially phenolic acids such as ferulic acid and smaller amounts of flavonoids and lignans), alkylresorcinols, phytic acid, betaine, total choline-containing compounds, inositols, phytosterols, policosanol and melatonin. Each one of these compounds has numerous physiological functions and recognised health benefits (Tables 3 and 4). While studying each compound separately, the main approach used to date, may well be unavoidable, it also involves considerable risk. This is because it ignores two important factors. One is the importance of synergy between the actions of compounds which is poorly characterised and more difficult to assess than the biological action of an isolated compound. The second is the importance of the cereal matrix and its influence on the accessibility of compounds in the digestive tract and hence on their availability within the organism. Indeed, little is often known of the bioavailability of many bioactive compounds derived from complex cereal products (Table 2). Thus, the amount of a particular compound in

Table 1. Average content of the major bioactive compounds in whole-grain wheat and wheat bran and germ fractions (%)*

Bioactive compound	Whole-grain wheat†	Wheat bran†	Wheat germ†
α-Linolenic acid (18 : 3*n*-3)	−‡	0·16	0·53
Sulfur compounds	0·5	0·7	1·2
Total free glutathione§	0·007	0·038	0·270
Dietary fibre‖	13·2	44·6	17·7
Lignins	1·9	5·6	1·5
Oligosaccharides¶	1·9	3·7	10·1
Phytic acid	0·9	4·2	1·8
Minerals and trace elements	1·12	3·39	2·51
Vitamins	0·0138	0·0398	0·0394
B vitamins	0·0091	0·0303	0·0123
Vitamin E (tocopherols and tocotrienols)	0·0047	0·0095	0·0271
Carotenoids	0·00 034	0·00 072	−‡
Polyphenols	0·15	1·10	>0·37
Phenolic acids	0·11	1·07	>0·07
Flavonoids	0·037	0·028	0·300
Lignans	0·0004	0·0050	0·0005
Alkylresorcinol	0·07	0·27	−‡
Betaine	0·16	0·87	0·85
Total choline	0·12	0·17	0·24
Total free inositols (*myo*- and total *chiro*-inositols)	0·022	0·025	>0·011
Phytosterols	0·08	0·16	0·43
Policosanol + melatonin + *para*-aminobenzoic acid	0·00 341	0·00 290	>0·00 186
Total	>15·4	51·5	>23·9
Subtotal (without dietary fibre)	>2·2	6·9	>6·2

* Mean percentages of bioactive compounds found in wheat bran, whole-grain wheat and wheat germ are calculated from Table 2 as follows: % = (minimum value + maximum value)/2.
† Expressed as g/100 g food.
‡ No data found.
§ Total free glutathione is given as glutathione equivalents = reduced glutathione + (oxidised glutathione × 2).
‖ Dietary fibre content is measured according to the AOAC method as such or modified (for details, see American Association of Cereal Chemists[53]).
¶ Oligosaccharides include fructans, raffinose and stachyose.

whole-grain cereals is rarely the same as the amount that is available to exert a given physiological action, in contrast to the result of consuming the free compound.

There may be many protective physiological mechanisms associated with consuming whole-grain cereal because of the high number of protective compounds. They may be mechanical within the digestive tract (insoluble fibre can increase transit time and faecal bulking), hormonal (Zn, Se and nicotinic acid participating in hormone activation and synthesis), antioxidative (almost all micronutrients), anti-inflammatory (for example, *n*-3 α-linolenic acid, Cu and ferulic acid), anti-carcinogenic (almost all micronutrients), or linked to gene regulation (for example, flavonoids), cell signalling (for example, polyphenols and redox status), energy metabolism (for example, the B-complex vitamins) and effects on enzymes (for example, some minerals and trace elements) (Table 3).

The main objective of the present paper is to propose new hypotheses for exploring the mechanisms behind the protective actions of whole-grain cereals using wheat as the main example. I have therefore exhaustively itemised all the bioactive compounds in whole-grain wheat and in the two fractions that are usually removed during refining: bran and germ. I have also listed their contents (range) in wheat, their bioavailability when obtained from complex whole-grain wheat products, their potential physiological effect(s) and the resulting health outcomes, with particular attention to some compounds that are specific to cereals other than wheat. The proposed new hypotheses are based on the action of compounds that are all bioactive when tested alone in their free form, such as the B vitamins, lignin, phytic acid, betaine, choline-containing compounds, inositols, policosanol, melatonin, *para*-aminobenzoic acid, sulfur amino acids, α-linolenic acid, phytosterols and some oligosaccharides.

First, I define the term 'whole-grain cereal products' and then examine the presently accepted mechanisms for explaining the role played by whole-grain cereals in preventing chronic diseases, as identified by studies on human subjects (for example, the importance of food structure and antioxidants), on rats (for example, the anti-carcinogenic property of many phytochemicals) and *in vitro* (cell-associated mechanisms). I then discuss my new hypotheses that are based on recent findings and on the potential physiological effects of whole-grain cereal compounds. I develop a broader view of the well-known antioxidant hypothesis that takes into account the actions of polyphenols on cell signalling and gene regulation in relation to the redox status. I review recent publications that have also revealed the great potential of the nutrigenomic approach for extending our knowledge of the protective mechanisms associated with complex foods. Finally, I briefly review the ways by which the nutritional quality of cereal products can be improved so as to optimally preserve the protective properties of whole-grain cereals.

What are whole-grain cereal products?

Definition

The American Association of Cereal Chemists (AACC) gave the following scientific and botanical definition in 1999: 'Whole grains shall consist of the intact, ground, cracked or flaked caryopsis, whose principal anatomical

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Table 2. Content, apparent absorption and fermentability of bioactive compounds and fibre from whole-grain wheat and wheat bran and germ fractions*

Bioactive compound	Content in whole grain (per 100 g)†	Apparent absorption or degree of fermentation in crude or processed whole-grain wheat (%)	Content in bran (per 100 g)†	Apparent absorption or degree of fermentation in crude or processed wheat bran (%)	Content in germ (per 100 g)†
n-3 Fatty acids (g/100 g)					
α-Linolenic acid (18 : 3*n*-3)	–‡	–‡	0·16	–‡	0·47–0·59
Sulfur compounds					
Reduced glutathione (mg/100 g)§	1·04–5·74	Negligible in humans when free‡	1·7–19·4	Negligible in humans when free‡	19·4–245·7
Oxidised glutathione (mg/100 g)§	0·86–2·88	–	6·1–21·4	–	15·3–122·4
Methionine (g/100 g)	0·17–0·24	–	0·20–0·29	–	0·39–0·58
Cystine (g/100 g)	0·19–0·40	–	0·32–0·45	–	0·35–0·61
Sugars (g/100 g)					
Monosaccharides	0·26–1·30	–	0·14–0·63	–	0·6–1·5
Sucrose	0·60–1·39	–	1·8–3·4	–	7·7–16·0
Fibre (g/100 g)					
Total	9·0–17·3	34 in humans‖	35·7–53·4	34–56 in humans; 37–49 in rats; 42–65 in pigs‖	10·6–24·7
Insoluble	9·5–11·4	–	32·4–41·6	42 in rats‖	8·5–18·6
Soluble	1·1–3·2	–	1·3–5·8	73 in rats‖	2·1–6·1
Cellulose	2·1–2·8	20 in humans‖	6·5–9·9	6–23 in humans; 14–24 in pigs and rats‖	7·5
Hemicellulose	8·6	46 in humans‖	20·8–33·0	50–54 in humans; 47–74 in pigs and rats‖	6·8
Lignins	0·9–2·8	4 in humans‖	2·2–9·0	0 in humans‡; 0–4 in rats‖	1·3–1·6
Fructans	0·6–2·3	–	0·6–4·0	–	1·7–2·5
Raffinose	0·13–0·59	97–99 in dogs fed a soyabean meal‡	1·08–1·32	Almost completely fermented when free‡	5·0–10·9
Stachyose	0·05–0·17	97–99 in dogs fed a soyabean meal‡	0·04–0·36	Almost completely fermented when free‡	–
Arabinoxylans	1·2–6·8	–	5·0–26·9	49 arabinose in humans; 71 xylose in humans	5·6–9·1
Water-extractable	0·2–1·2	–	0·1–1·4	–	0·4
β-Glucans	0·2–4·7	–	1·1–2·6	–	–
Phytic acid (hexakisphosphate; g/100 g)	0·3–1·5	Poorly absorbed in humans; 54–79 degraded in human subjects fed whole bread; 79 % absorbed as free compound in rats‡¶	2·3–6·0	58–60 degraded into lower inositol phosphates in ileostomates fed raw wheat bran	1·4–2·2
Minerals (mg/100 g)					
Fe	1·0–14·2	1–20 in human or usual diets‡	2·5–19·0	3·8 in human subjects fed wheat bran rolls	3·9–10·3
Mg	17–191	21–28 in human subjects fed brown bread diet; 70 in rats	390–640	–	200–290
Zn	0·8–8·9	17–20 in humans; 19–95 in rats	2·5–14·1	–	10–18
Mn	0·9–7·8	Very low‡	4–14	Very low‡	9–18
Cu	0·09–1·21	62–85 in humans; 16 as free compound in rats	0·84–2·20	–	0·70–1·42
Se	0·0003–3	81–85 in rats	0·002–0·078	60–80 in rats/free sodiumselenite	0·001–0·079
P	218–792	41–55 in humans fed brown bread diet	900–1500	41–56 in human subjects fed sodium phytate‡	770–1337
Ca	7–70	82 % in humans; 43–93 in rats	24–150	22 % in humans	36–84
Na	2–16	–	2–41	–	2–37
K	209–635	–	1182–1900	–	788–1300
Vitamins (mg/100 g)					
Thiamin (B_1)	0·13–0·99	91 in rats/free thiamin mononitrate	0·51–0·80	–	0·8–2·7

Riboflavin (B_2)	0·04–0·31	95 as oral supplement in human subjects‡	0·21–0·80	–	0·50–0·80
Nicotinic acid (B_3)	1·9–11·1	Low, since mostly bound‡	13·6–35·9	27–38 in humans (nicotinic acid concentrate)	4·0–8·5
Pantothenic acid (B_5)	0·7–2·0	About 50 in human/average American diet‡	2·2–4·1	–	1–2·7
Pyridoxine (B_6)	0·09–0·66	71–79 in human/average American diet as compared with free compound‡	0·70–1·30	Unavailable in humans	0·49–1·98
Biotin (B_8)	0·002–0·011	Very low‡	0·0440	Very low‡	0·0172
Folate (B_9)	0·014–0·087	–	0·088–0·373	Low	0·14–0·70
Tocopherols + tocotrienols (E)	2·3–7·1	–	9·5	Not readily available	23·1–31
Total tocopherols	1·06–2·89	–	2·4	–	21·5–30·6
α-Tocopherol	0·34–3·49	70 in humans as free compound	0·13–2·84	–	3·1–22
Total tocotrienols	1·09–4·49	–	7·10	–	1·3–1·6
Phylloquinone (K)	0·002–0·020	–	0·002–0·083	–	0·003–0·350
Carotenoids (mg/100 g)					
Total	0·044–0·626	–	0·25–1·18	–	–
β-Carotene	0·005–0·025	–	0·003–0·010	–	0·062
Lutein	0·026–0·383	–	0·050–0·180	–	–
Zeaxanthin	0·009–0·039	–	0·025–0·219	–	–
β-Cryptoxanthin	0·001–0·013	–	0·018–0·064	–	–
Polyphenols					
Phenolic acids (mg/100 g)**					
Total	16–102	See free/soluble-conjugated and bound‡	761–1384	See free/soluble-conjugated and bound‡	–
Extractable (free and conjugated)	5–39	Probably high	46–63††	Probably high	51
Bound	14–78	See wheat bran‡	148–340††	33 in pig; partially/slowly solubilised within human model colon	–
Ferulic acid (mg/100 g)					
Total	16–213	Low: 3·4 % urinary excretion in rats	138–631	Low: 2·0–5·7 % urinary excretion in humans and 3·9 % urinary excretion in rats	7–124
Extractable (free and conjugated)	0·7–4·9	High in rat small intestine	1·3–23·1	High: 27·8–78·9 % urinary excretion in humans; high in rat small intestine	18
Bound	14–64	Low: action of small intestine esterases	122–286	Low: action of small intestine esterases	–
Dehydrodiferulic acid	1·5–76·0	See wheat bran‡	13–230	Undetectable in human plasma; free diferulic acid can be absorbed from the gut in rats	9
Dehydrotrimer ferulic acid	2·6–3·5	–	15–25	–	–
Flavonoids (mg/100 g)	30–43‡‡	–	15–41	–	300§§
Free (mg/100 g)	2·2–4·9‡‡	–	–	–	–
Bound (mg/100 g)	28–40‡‡	–	–	–	–
Anthocyanins (mg/100 g)	0·5–52·4	–	0·9–48·0	–	–
Isoflavonoids (μg/100 g)	14·8‖‖	–	3·8–10·4	–	–
Lignans (mg/100 g)	0·2–0·6	–	2·8–6·7	–	0·49
Others					
Alkylresorcinols (mg/100 g)	12–129	60–79 in pig small intestine fed whole-grain rye bread	215–323	45–71 % from ileostomy effluents in humans fed rye bran soft/crisp bread	–
Betaine (mg/100 g)	22–291	–	230–1506	–	306–1395
Total choline¶¶ (mg/100 g)	27–195	–	74–270	–	152***–330
Phytosterols (mg/100 g)	57–98	Weakly absorbed from the gut‡	121–195	Weakly absorbed from the gut‡	410–450
Inositols					
Total *chiro*-inositol††† (mg/100 g)	17	Apparently high in humans/free compound	nd	–	–
Free *myo*-inositol (mg/100 g)‡‡‡	1·9–7·5	Apparently high in rat as free compound	14·0–36·4	–	8·5–13·3

Table 2. *Continued*

Bioactive compound	Content in whole grain (per 100 g)†	Apparent absorption or degree of fermentation in crude or processed whole-grain wheat (%)	Content in bran (per 100 g)†	Apparent absorption or degree of fermentation in crude or processed wheat bran (%)	Content in germ (per 100 g)†
Policosanol (mg/100 g)	0·30–5·62	–	0·11–3·00	–	1·01
Melatonin (μg/100 g)	0·2–0·4	–	–	–	–
p-Aminobenzoic acid (mg/100 g)	0·34–0·55	–	1·34	–	0·85

nd, Not detected.
* All data are based on international references unless specified (see references in Appendices); for bioavailability data, methods used for determining percentage apparent absorption, the subject status and the model used (animals *v.* humans) differ from one study to another which may explain the sometimes very large range of values given: data remain therefore indicative and should be taken cautiously.
† When expressed on a DM basis in references, results were converted on a wet matter basis considering that whole grain, bran and germ contain 13, 10 and 11·4 g water/100 g food, respectively.
‡ No data found as regard with whole-grain wheat, and wheat bran and germ.
§ Total glutathione equivalents = reduced glutathione + (oxidised glutathione × 2).
‖ Degree of fermentation.
¶ Small-intestinal phytases (high activity in rats and very much lower in humans and pigs) are able to hydrolyse phytic acid.
** High ranges are likely to result from the different types of extraction procedure used.
†† Expressed in gallic acid equivalents/100 g.
‡‡ Expressed in catechin equivalents.
§§ Expressed as rutin equivalents.
‖‖ Sum of genistein and daidzein (whole-wheat flour type not specified).
¶¶ Total choline refers to the sum of free choline, glycerophosphocholine, phosphatidylcholine and sphingomyelin.
*** Toasted wheat germ[477].
††† *Chiro*-inositol refers to the sum of free D-*chiro*-inositol and *chiro*-inositol moieties mainly derived from pinitol (i.e. methyl *chiro*-inositol) and glycosylated pinitol.
‡‡‡ Evaluation based on the fact that about 95 % of total *myo*-inositol would come almost exclusively from phytic acid[250].

components – the starchy endosperm, germ and bran – are present in the same relative proportions as they exist in the intact caryopsis'[20]. The definition given by the Whole Grains Council in May 2004 includes processed food products: 'Whole grains or foods made from them contain all the essential parts and naturally-occurring nutrients of the entire grain seed. If the grain has been processed (e.g. cracked, crushed, rolled, extruded, and/or cooked), the food product should deliver approximately the same rich balance of nutrients that are found in the original grain seed'[21]. The US Food and Drug Administration published a Draft Guidance on Whole-grain Label Statements in 2006 that adopted the international AACC definition and included amaranth, barley, buckwheat, bulgur, maize (including popcorn), millet, quinoa, rice, rye, oats, sorghum, teff, triticale, wheat and wild rice; pearled barley was not included because some outer layers of the bran fraction are removed[22]. Pseudocereals such as amaranth, buckwheat and quinoa have similar macronutrient compositions (carbohydrates, proteins and lipids), and are used in the same traditional ways as cereals[23,24]. The response to the US Food and Drug Administration Draft Guidance by the AACC International recommended that some traditional cereals such as 'lightly pearled barley, grano (lightly pearled wheat), nixtimalized corn and bulgur that has been minimally processed be also classified as whole grains'[23], making allowance for small losses of components that occur through traditional processing. The Whole Grain Task Force stated in 2008 that it 'supports the use of the term whole-grain for products of milling operations that divide the grain into germ, bran and endosperm, but then recombine the parts into their original proportions before the flour leaves the mill'[24]. However, as I will explain later, most of the products defined as whole-grain foods in studies showing the health benefits of whole-grain cereals are made of recombined whole-grain flours[24], which rarely contain the same proportions of bran, germ and endosperm as the intact grain before milling. Thus, the germ fraction is almost always removed because its high lipid content (about 9 %) may go rancid upon storage[25]. Processing whole-grain cereals also leads to losses of bioactive compounds so they cannot really deliver 'approximately the same rich balance of nutrients that are found in the original grain seed'[21]. Thus, if researchers had referred strictly to the definitions given above, few studies could have concluded that whole-grain cereal foods protect human health. Alternative definitions have therefore been proposed by the Whole Grain Task Force in which 'as they exist in the intact caryopsis' in the AACC definition is replaced by 'as found in the least-processed, traditional forms of the edible grain kernels' or completed by adding 'as they exist in the intact caryopsis to the extent feasible by the best modern milling technology'[24]. This last definition is probably the best adapted to our Western country technologies. But none of these alternative definitions has been adopted to date and there is still no official international definition of whole-grain cereal products in Europe.

What proportions?

Finally, the proportion of whole grains that must be present in a cereal product needs to be defined for it to be considered

Table 3. Main physiological functions, potential protective mechanisms and health benefits of isolated bioactive compounds found in whole-grain wheat, rice and oat*

Bioactive compounds (degree of significance)	Main physiological functions and potential protective mechanisms	Potential health protection
n-3 Fatty acids		
α-Linolenic acid (18 : 3*n*-3) (++)	Beneficial effects on blood clotting, thrombosis, blood pressure and inflammation: for example, anti-atherosclerotic effect via inhibition of oxidative stress-mediated CD40L (protein with inflammatory and prothrombotic property) up-regulation, suppresses levels of arachidonic acid (20 : 4*n*-6) and eicosanoids in tissues (such as lung) and plasma phospholipids and the synthesis of pro-thrombotic cyclo-oxygenase-derived products (thromboxane A2 and B2, PGE2), reduces plasma TAG, inhibits synthesis of cytokines and mitogens; essential constituent of neuronal cells and retina; precursor *in vivo* of potentially protective DHA (22 : 6*n*-3) and EPA (20 : 5*n*-3); stimulates immune system via cell signalling and gene expression	CVD; retinal and brain development; inflammatory bowel disease (Crohn's); breast and colon cancers; mild hypertension; mental health (for example, depression and anxiety); rheumatoid arthritis
Sulfur compounds		
Reduced glutathione GSH (+)	Strong antioxidant; detoxification of toxic electrolytic metabolites of xenobiotics and of reactive oxygen intermediates generated intracellularly and at sites of inflammation; binding with cellular mutagens; important role in cellular immune function and as source of cysteine for various organs	Some cancers (for example, oral); diseases associated with imbalance of glutathione (for example, HIV, ageing, hepatic cirrhosis, cystic fibrosis and lung and neurode-generative disorders)
Methionine (++)	Precursor of S-adenosyl methionine, the universal methyl donor, and of glutathione; intermediate in the biosynthesis of cysteine, carnitine, taurine, lecithin, phospha-tidylcholine, and other phospholipids; methyl donor; may possess antioxidant activity; lipotrope	Neural tube defects; cognitive impairment; atherosclerosis; muscular wasting
Cystine (+)	Reduced to two cysteine residues upon absorption; cell signalling through reactive cysteine residues in proteins; antioxidant; precursor of glutathione; constituent of the antioxidant metallothionein; many metal cofactors in enzymes are bound to the thiolate substituent of cysteinyl residues; precursor to Fe–S clusters (role in the oxidation–reduction reactions of mitochondrial electron transport); increases protein stability in the harsh extracellular environment	Muscular wasting; normal hair and nail development
Undigestible carbohydrates		
Insoluble fibre (+++)† (cellulose, hemicellulose)	Delivers antioxidant-bound phenolics to the colon; carcinogen binding and/or diluting; increases gut transit and faecal bulking; satiating effect	Gut health; colon cancer; obesity and weight regulation
Soluble fibre (++)† (for example, β-glucans, arabinoxylans)	Decreases glycaemia through a delayed gastric emptying and glucose absorption rate; reduces cholesterolaemia through a possible effect of propionate (yielded by fibre fermentation) upon hepatocyte cholesterol and NEFA synthesis; improves insulin response; reduces bile acid reabsorption; produces SCFA	Type 2 diabetes; CVD; gut health; colon cancer
Resistant starch (+++)†	Produces high levels of butyrate, a tumour-growth suppressor; decreases glycaemia, cholesterolaemia and energy intake; promotes lipid oxidation and metabolism; prebiotic effect	Type 2 diabetes; CVD; colon health and cancer; body weight; gallstones
Oligosaccharides (++) (fructans, raffinose, stachyose)	Prebiotic (effect on bacterial metabolism: for example, bifidogenic); cholesterol-lowering through SCFA production, especially propionate; decrease glycaemia (through reduced hepatic gluconeogenesis by propionate) and triacylglycerolaemia; limit TAG accumulation in liver: effect on lipogenesis through exposure to propionate and reduced insulin/glucagon levels; produce butyrate, a tumour-growth suppres-sor; increase the absorption of minerals within colon; stimulate the immune system; control blood ammonia levels	Gut health; colon cancer; CVD; lifespan; weight reduction; hepatic encephalopathy (nervous troubles) and steatosis
Phytic acid (+++) (also named *myo*-inositol hexakisphosphate)	Antioxidant: chelates various metals (for example, suppresses damaging Fe-catalysed redox reactions), inhibits xanthine oxidase, suppresses oxidant damage to the intestinal epithelium, and interferes with the formation of ADP-Fe-oxygen complexes that initiate lipid peroxidation; prevents the formation of carcinogens and blocks the interaction of carcinogens with cells; controls cell division and reduces cell proliferation rate; increases the immune response by enhancing the activity of natural killer cells; may be involved in cellular and nuclear signalling pathways; important source of P; inhibitor for renal stone development; hypoglycaemic (for example, by chelating Ca, an α-amylase cofactor) and cholesterol-lowering (by	Various cancers (for example, colon and breast cancers); type 2 diabetes; CVD (for example, age-related aorta calcification); kidney health (renal stone development); hypercalciura; acute Pb poisoning; dental caries

Table 3. *Continued*

Bioactive compounds (degree of significance)	Main physiological functions and potential protective mechanisms	Potential health protection
	binding Zn and decreasing Zn:Cu ratio) effects; affects the metabolic and detoxification capacity of the liver; reduces blood glucose and lipid, and hepatic lipid levels; inhibits calcification of cardiovascular system (lower level of Ca in aorta); prevention of platelet aggregation; high affinity for hydroxyapatite; adsorption onto Ca-based crystals; *in vitro* effect on gene expression through chromatin remodelling	
Lignins (+++)	Antioxidant due to phenolic hydroxyl groups; adsorb dietary carcinogens and reduce carcinogen exposure; reduce bile acid reabsorption as a bile salt-sequestrating agent: possibly reduce fat absorption and the formation of carcinogenic metabolites from bile salts, and increase cholesterol turnover; source of enterolactone, a phyto-oestrogenic mammalian lignan	Colon cancer; large bowel health; type 2 diabetes; CVD
Minerals and trace elements		
Fe (++)†	Cofactor with several enzymes involved in energy metabolism and thermoregulation: for example, catalase cofactor in the production of $O_2 + 2H_2O$ from H_2O_2, involvement in the Krebs cycle, oxygen transport as Hb and myoglobin constituent, and electron carrier within cytochromes; close association between the activities of Fe-containing oxidase pathways in muscle and endurance; role in collagen synthesis, and bone formation and resorption (for example, bone mineral density in post-menopause); role in cell-mediated immunity and phagocytosis; role in vitamin metabolism; improves developmental scores in Fe-deficient infants; might reduce increase in lipid peroxides and liver/serum TAG, cholesterol and phospholipids; deficiency associated with obesity	Mental health (fatigue, concentration, cognitive development and reduced intellectual performances); physical health (anaemia, reduced effort and resistance to infections); bone health
Mg (+++)†	Second most abundant intracellular cation; constituent of several metalloenzymes with a role in cellular functions: glycolysis, DNA transcription, protein synthesis and oxidative phosphorylation; essential for all ATPase activity; necessary for coenzyme A reaction (for example, increases enzyme activity in the liver: lipotrope-like effect); role in neurotransmission, gut transit/cardiac rhythm/blood pressure regulation, platelet aggregability and insulin sensitivity; improved glucose uptake, glucose metabolic clearance rate, and oxidative glucose metabolism; cholesterol-lowering and may reduce hypertriacylglycerolaemia; antioxidant (for example, against lipid peroxidation); favours Ca fixation in bones and muscle relaxing; activates alkaline phosphatase; psycho-relaxing; anti-inflammatory and anti-allergic effects; favours thermoregulation; important role in inducing some angiogenesis-related mechanisms; direct inhibition of calcium oxalate crystallisation in the urine	Mental health (fatigue, stress and anxiety); type 2 diabetes; CVD (for example, atherosclerosis and hypertension); bone health (skeletal growth and osteoporosis); nervous and muscular equilibrium; renal stones
Zn (++)†	Superoxide dismutase and alkaline phosphatase cofactor; antioxidant; chemical inactivator: inhibits the formation of active carcinogenic compounds (for example, conversion of nitrosamines from nitrite in the stomach and Zn-binding compounds); lymphocyte T and hormone activator; participates in numerous enzymic reactions (more than 200 enzymes) in relation to carbohydrate, lipid and protein metabolism; role in neurotransmission; DNA stabilisation; markedly modulates mechanisms of the pathology of inflammatory diseases; influences gene expression, cell development and replication; role in cell signalling within salivary gland, prostate, immune system, intestine and endothelial cells (for example, NF-κB and activator protein-1); key factor in reproductive organ growth; role of Zn homeostasis in insulin secretion/responsiveness; may stimulate food intake via orexigenic peptides coupled to the afferent vagal stimulation	Immunoprotection; brain and mental health; atherosclerosis; cancers (for example, oesophagus); skeletal growth and maturation; olfaction (anosmia); type 2 diabetes; weight regulation (for example, anorexia)
Mn (++)	Constituent of several metalloenzymes (for example, superoxide dismutase cofactor); role in amino acid, lipid and carbohydrate metabolism, insulin secretion and cholesterol synthesis; favours fat and sugar assimilation; improves cartilage elasticity and membrane quality of small blood vessels; protects vitamins (thiamin, biotin and vitamin E); role in synovial liquid formation; essential for growth and	Anti-ageing; vascular sclerosis; bone formation (for example, osteoporosis); cancers

	reproduction; anti-carcinogenic: manganese superoxide dismutase plays a role in regulating tumour cell growth and its over-expression suppresses NF-κB activation in carcinogenic process	
Cu (+)	Component of numerous metalloenzymes acting as oxidases to achieve the reduction of molecular oxygen (for example, superoxide dismutase cofactor, lysyl oxidase or cytochrome *c* oxidase); anti-inflammatory and anti-infectious effects; role in neurotransmission, and Hb and collagen fibre synthesis; reverses cardiomyocyte hypertrophy; anti-cancer effect of Cu–DNA complexes (for example, with guanine). Role in well-balanced cholesterolaemia and glucose tolerance; antioxidant effect mainly as superoxide dismutase cofactor; low Zn:Cu ratio associated with reduced risk of CHD	Brain and mental health (central nervous system dysfunction); bone, tendon and cartilage health (for example, osteoarthritis); cardiovascular health (for example, IHD); cancers
Se (++)†	Glutathione peroxidase/thioredoxin reductase cofactor: protects cell membranes from lipid oxidation damage; role at the catalytic site of multiple selenoproteins; tumour growth suppressor (selective apoptotic activity according to the tissue considered); reduces susceptibility to experimental carcinogens; immune system stimulation and role in anti-infective mechanisms; helps liver to eliminate toxins; role thyroid hormone synthesis; may improve insulin resistance and protect vascular endothelium; insulin-like actions; prevents platelet aggregation	Anti-ageing; CVD; immunoprotection; breast, prostate, gastrointestinal, liver, brain, skin and lung cancers; liver health; type 2 diabetes
P (++)†	Most abundant mineral after Ca within organism (80 % is in skeleton, 10 % in muscles and 10 % in nervous tissues and blood); supports tissue growth through temporary storage and transfer of energy (for example, ATP/ADP), helps in maintaining normal pH (acidity regulation through buffering effect) and activation of many catalytic proteins by phosphorylation; limits Ca escape and its metabolism; DNA/RNA, myelin and hydroxyapatite constituent; occurs structurally as phospholipids (for example, lecithin), a major component of most biological membranes; stimulates B-complex vitamins; may reduce the risk of colorectal tumours	Bone (for example, osteoporosis), teeth, mental (for example, fatigue, spasmophily, stress, memory, vigilance) and brain health; heart and kidney health; digestion and growth; cancers (for example, colorectal)
Ca (+)†	Most abundant mineral within organism (about 98 % in bones as hydroxyapatite); role in bone and teeth formation, cellular exchanges, nerve transmission, blood coagulation, muscle contraction (for example, in heart), pH regulation, P retention and glandular secretion; essential signal transduction element (for example, cell cycle progression regulation); intracellular Ca is vital for regulation of cell proliferation and growth; may reduce systolic blood pressure; enzyme activation; role in vitamin B_{12} assimilation, blood acid–base equilibrium and clotting, Fe metabolism and immune system maintenance; inversely associated with type 2 diabetes; would regulate fat metabolism in adipocytes	Bone (for example, osteoporosis and rachitis) and teeth health; colorectal cancer; heart health (for example, hypertension and stroke); nervous system; mental health (for example, insomnia and stress); diabetes; weight regulation
Na (+)†	50 % of Na is in extracellular liquids; generally associated with chlorine (NaCl); role in nervous and muscular impulse transmission, in control of arterial pressure and acidity regulation; role in water repartition within organism: essential in hydroelectric equilibrium by yielding most part of extracellular liquid osmotic pressure	CVD (for example, blood pressure); nervous system; hydration state
K (++)†	Cation essentially intracellular; role in acid–base equilibrium; favours Na excretion; inhibition of neuromuscular excitability; role in regulation of aldosterone excretion within glomerular zone; role in action of numerous enzymes; role in gastric acid and insulin secretion, and in blood pressure regulation; improves ventricular arrhythmia; may have inhibitory effects on free radical formation from macrophages and endothelial cells and on LDL oxidation, vascular smooth muscle cell proliferation (for example, neointima formation) and arterial thrombosis; reduces platelet sensitivity to thrombin; may reduce macrophage adherence to vascular wall; role in glucose control	Muscular contraction (for example, cramps); hydration state; cardiovascular protection and nervous system functioning; mental health (for example, vigilance and fatigue); oedema; hypercalciura; osteoarthritis/porosis; arterial hypertension; kidney health (for example, stones); cerebro/cardiovascular diseases; type 2 diabetes
Vitamins		
Thiamin: B_1 (++)	Involved in glucose metabolism and Krebs cycle through thiamin-dependent enzymes, and in branched-chain amino acid metabolism; works to promote healthy nerves (for example, neuromodulation of chlorine canals in brain and involvement in neurotransmitter synthesis); improves mood; strengthens the heart and may restore peripheral vascular resistance; improves heartburn; antioxidant	Mental (for example, Korsakoff syndrome and dry Beri Beri), neuronal (for example, neuropathy) and heart (for example, wet Beri Beri) health

Table 3. *Continued*

Bioactive compounds (degree of significance)	Main physiological functions and potential protective mechanisms	Potential health protection
Riboflavin: B_2 (++)†	Participates as a coenzyme in numerous redox reactions in metabolic pathways and energy production via the respiratory chain; assists fat, protein and carbohydrate metabolism; role in haematological status (erythrocyte formation) and gastrointestinal development; modulator of plasma homocysteine level; protects from heart tissue damage; improves skin blemishes and migraines; influence dark adaptation through riboflavin-dependent photoreceptors; participates in antioxidant defences; possibly anti-carcinogenic (for example, reduction in DNA damage)	CVD; cancers; vision (for example, corneal opacity and cataract); mental health (for example, neurodegeneration and peripheral neuropathy); skin health
Nicotinic acid: B_3 (++)†	Precursor of nicotinamide, NAD +, NAD, NADP, NADH, and NADPH: functions in many redox reactions; lowers cholesterol, LDL and NEFA levels and increases HDL level; inhibits catecholamine stimulation of lypolysis in adipose tissue (via the same post-receptor pathway as catecholamines); involved in DNA replication and repair, in cell differentiation and the production of steroid hormones in the adrenal gland	Skin health (for example, dermatitis in pellagra); lipid disorders and CVD; cancers; HIV; mental health (for example, schizophrenia, depression, insomnia); osteoarthritis
Pantothenic acid: B_5 (++)†	Ubiquitous vitamin; critical in the metabolism and synthesis of carbohydrates, proteins, and fats; used in the synthesis of coenzyme A, a way to transport carbon atoms within the cell (cellular respiration); involved in metabolism of fatty acids (biosynthesis), cholesterol and acetylcholine; would enhance the activity of the immune system	Cure of wounds, minor burns, irritations and cutaneous hurts; mental health (for example, insomnia, depression, irritability and stress); healthy digestive tract
Pyridoxine: B_6 (++)†	Needed for almost every function in the body, working as a coenzyme for numerous enzymes, notably in protein, glycogen, sphingoid bases, amino acid and fat/fatty acid metabolism; plays a major role in forming erythrocytes, neurotransmitters (such as serotonin, melatonin, dopamine and γ-aminobutyric acid) and in antibody synthesis; stabilises homocysteine levels; allows production of nicotinic acid from tryptophan; role in vitamin B_{12} absorption; role in humoral and cellular immunity; role in maintenance and synthesis of DNA	Heart health; mental and brain health (for example, depression, fatigue, insomnia and epileptiform convulsions); colorectal cancer; asthma attacks; microcytic anaemia; occlusive arterial disease; seborrhoeic dermatitis
Biotin: B_8 (++)†	Functions as a coenzyme in bicarbonate-dependent carboxylation reactions (i.e. for four carboxylase enzymes such as the acetyl-CoA carboxylase): catalysis for CO_2 fixation on different substrates fundamentally involved in lipid, protein and carbohydrate assimilation; necessary for cell growth and the production of fatty acids; role in the citric acid cycle; helps to maintain a steady blood sugar level; regulation of gene expression; role in normal immune function and cell proliferation (oncogene-dependent metabolic pathways)	Mental and central nervous system health (neurological disorders); growth; skin health (for example, dermatitis); hair health (for example, alopecia)
Folate: B_9 (+)†	Functions as a coenzyme in single-carbon transfers in the metabolism of nucleic and amino acids: stabilises homocysteine levels, needed to synthesise DNA bases and for DNA replication; anti-carcinogenic; prevents depletion of brain membrane phosphatidylcholine; lipotrope; effect on altered methylation and related epigenetic effects on gene expression	Neural tube defects; CVD; cancers (for example, colon); fertility; megaloblastic anaemia; mental health (cognitive impairment and depression)
Tocols: E (++)†	Strong intracellular antioxidant that protects from oxidative damages of PUFA within cell membranes and in lipoproteins, DNA nucleotidic bases and proteins; complementary effect with Se to maintain cell integrity and immune function; induction of apoptosis (anti-proliferative effect); anti-atherogenic action through, for example, reduction of oxidised LDL and of monocytes adhesion or inhibition of smooth muscle cell proliferation	–
Tocopherols	Antioxidant; act directly to inhibit the formation of active carcinogenic compounds or their activation to more potent forms; possible protection of pancreatic β-cells against glucose toxicity; various non-antioxidant molecular mechanisms: inhibit protein kinase C (correlation with cell proliferation inhibition), produce a decrease in monocyte superoxide anion and IL-1 release and in adhesion to endothelium, effect on gene expression (possible direct action on cell signalling), and remove the suspected carcinogens peroxynitrite-derived nitrating species	Cancers (for example, pancreas); CVD; type 2 diabetes

Tocotrioenols	Stronger antioxidant than tocopherols; role in immune response induction and bone calcification; prevent the formation of carcinogens (anti-proliferative and apoptotic inducer); cholesterol-lowering; anti-hypertensive; anti-inflammatory; anti-atherogenic; may increase bone Ca content	Neurodegeneration; cancers; CVD; type 2 diabetes; osteoporosis; obesity
Phylloquinone: K (+)	Functions as a coenzyme involved in the post-translational formation of γ-carboxyglutamate residues, essential for the activity of all known γ-carboxyglutamate proteins, which plays a role in coagulation (for example, vitamin K-dependent clotting factors such as prothrombin – factor II and factors VII, IX and X), bone metabolism (probable role in Ca uptake) and vascular biology; in the intestines, assists in converting glucose to glycogen; anti-haemorrhagic factor	Bone health (osteoporosis and bone loss); atherosclerosis; haemorrhagic event and haematuria (reflects tumours or kidney stones?)
Carotenoids		
β-Carotene (+)†	Antioxidant; precursor of vitamin A; tumour growth suppressor (i.e. apoptosis inducer)	Colon cancer; lung cancer in non-smokers; coronary artery disease
Lutein (++)	Antioxidant by quenching single oxygen, neutralising photosensitisers and inhibiting lipid peroxidation; inhibits progression of aberrant crypt foci; protects ocular functions as antioxidant/optical filter and by increasing macular pigment density; reduces the skin inflammatory response; can inhibit thickening of the carotid artery walls and LDL-induced migration of monocytes to artery cell walls	Visual function protection (for example, age-related macular degeneration, cataract and glaucoma); stroke and atherosclerosis; lung and colon cancer; skin health
Zeaxanthin (+)	Antioxidant by quenching single oxygen, neutralising photosensitisers and inhibiting lipid peroxidation; reduces the skin inflammatory response; protects ocular functions as antioxidant/optical filter and by increasing macular pigment density	CVD (for example, stroke); visual function protection (for example, cataract); skin health; lung cancer
β-Cryptoxanthin (+)	Antioxidant; induces anabolic effects on bone components by increasing Ca content and alkaline phosphatase activity; possible protector against carcinogenesis (for example, bioregulatory function in the control of cell differentiation and apoptosis); precursor of vitamin A, retinal and retinoic acid	Bone loss; lung cancer; visual function
Polyphenols		
Phenolic acid (+++) (for example, ferulic acid)	Antioxidant (for example, scavenges superoxide anion radical and reduces oxidative stress caused during diabetes, for example, lipid peroxidation); anti-apoptotic; antimicrobial; anti-inflammatory; blood cholesterol- and glucose-lowering; UV absorber; interferes with intracellular signalling pathways; hypotensive effect by reducing blood pressure (vascular relaxation); tumour growth suppressor; enzyme modulator; may increase β-cell mass; may decrease adipose tissues, serum lipid profiles, insulin and leptin	Cancer; CVD (for example, thrombosis and atherosclerosis); neurodegenerative disorders (for example, Alzheimer's and Parkinson's diseases); type 2 diabetes; skin health; anti-ageing; hepatoprotective; pulmonary protective; hypertension; obesity
Flavonoids (+) (for example, anthocyanins, isoflavonoids)	Antioxidant (for example, against LDL-cholesterol oxidation); tumour growth suppressor; enzyme modulator; role in redox cell signalling, glutathione synthesis regulation and gene regulation; modulate angiogenesis; anti-microbial and anti-inflammatory; inhibition of platelet aggregation (for example, may affect arachidonic acid metabolism through inhibition of lipoxygenase activity); stimulation of uric acid production; role in fat oxidation and decreased adipose tissues; may decrease serum lipid profiles, insulin and leptin; hypoglycaemic effect; daidzein and/or genistein may improve trabecular connectivity and trabecular thickness	Cancer; CVD; body-weight regulation/obesity; type 2 diabetes; bone development and osteoporosis
Lignans (++)	Antioxidant: may reduce fatty acid oxidation; precursors of enterolactone and enterodiol; anti-carcinogenic activity: inhibit cell proliferation by competing with oestradiol for nuclear type II oestrogen-binding sites, stimulation of differentiation, may inhibit the tyrosine-specific protein kinase (associated with cellular receptors for several growth factors) and DNA topoisomerase, prevent the production of oestrone from androstenedione, and influence cholesterol homeostasis (for example, deoxycholic acid is correlated with increased colon cancer); anti-atherosclerotic; hypolipidaemic effect (improves blood lipid profile); diuretic action and antagonistic action of platelet-activating factor receptor; priming action on superoxide production on human neutrophiles; anti-bacterial and anti-fungal; may inhibit bone resorption	Colon cancer; hormonally mediated diseases (for example, breast and prostate cancers); CVD (for example, stroke); osteoporosis and rheumatoid arthritis; gastric and duodenal ulcers; skin health
Other compounds		
Alkylresorcinols (+++)	Antioxidant (for example, modulator of lipid oxidation); anti-microbial, anti-parasitic and anti-carcinogenic properties; inhibitors of 3-phosphoglycerate dehydrogenase (key enzyme of TAG synthesis in adipocytes); direct effect on structure and metabolism of nucleic acids; can be incorporated into biological membranes (for example,	Cancer; tuberculosis; tropical diseases

Table 3. *Continued*

Bioactive compounds (degree of significance)	Main physiological functions and potential protective mechanisms	Potential health protection
	modulate phospholipid bilayer properties by inhibiting the activity of some membrane-bound enzymes); cholesterol-lowering in liver	
Betaine (+++)	Osmoprotectant; methyl donor: increases DNA methylation and decreases hyperhomocysteinaemia; role in sulfur amino acid homeostasis; antioxidant; able to reverse insulin resistance; inversely associated with serum non-HDL-cholesterol, TAG, BMI, percentage body fat, systolic and diastolic blood pressure, and positively associated with HDL-cholesterol; inversely associated with inflammatory markers related to atherosclerosis (C-reactive protein and TNF-α); inverse association with colorectal adenoma; lipotrope	CVD; liver and kidney health; colorectal cancer; athletic performances; type 2 diabetes; metabolic syndrome
Choline (++)	Precursor of betaine, acetylcholine (neurotransmitter), membrane phospholipids (phosphatidylcholine and sphingomyelin: role in intracellular signalling) and platelet-activating factor (potent messenger molecule); methyl donor (for example, DNA methylation and reduced hyperhomocysteinaemia); epigenetic regulator of gene expression; promotes carnitine conservation (for example, accretion in skeletal muscle); antioxidant-type action; lipotrope: role in lipid metabolism (for example, increases fatty acid oxidation), and in integrity and signalling functions of cell membranes; accelerates the synthesis and release of acetylcholine	Brain development and normal learning and memory functions; weight regulation; fetal development (for example, neural tube); liver dysfunctions (for example, fatty liver); cancer; CVD
Phytosterols (++) (for example, β-sitosterol)	Lower serum total and LDL-cholesterol: compete with cholesterol for micelle formation in the intestinal lumen (and increase its excretion) and inhibit dietary and biliary cholesterol absorption; anti-inflammatory; may protect from vascular smooth muscle cell hyperproliferation; effect on immune system (for example, may prevent immunosuppression associated with excessive physical stress, i.e. immune-modulatory activity on human lymphocytes); β-sitosterol inhibits carcinogen-induced neoplasia (suppressing agent) and might mediate apoptosis through caspase activation; hypoglycaemic; anti-pyretic	CVD; colon, breast and benign prostate cancer; type 2 diabetes
Inositols (++) (for example, *myo*- and *chiro*-inositol, pinitol)	Involved in several biological processes as secondary messenger molecules: in insulin signal transduction, cytoskeleton assembly, nerve guidance, intracellular Ca concentration control, gene expression and breakdown of fat and reducing of blood cholesterol; *myo*-inositol may be converted into *chiro*-inositol *in vivo* (epimerisation) and is precursor for several phospholipids (for example, phosphatidylinositol 4-phosphate) playing a role in membrane structure and function; *chiro*-inositol improves insulin resistance and helps in controlling blood glucose, ovulatory functions (i.e. increased ovulation), decreases serum androgen and plasma TAG concentrations, and reduces blood pressure; *myo*-inositol depresses the rise in TAG and total lipid liver, hepatic activities of glucose-6-phosphate dehydrogenase, malic enzyme, fatty acid synthetase and citrate cleavage enzyme; free inositol is involved in volume regulation during persistent osmotic stress; reduces myelinolysis after rapid correction of chronic hyponatraemia; may reduce mammary and colon carcinoma; impaired *myo*-inositol metabolism would be linked to altered nerve conduction impairment in diabetics; prevents impaired sciatic nerve Na-K ATP	Type 2 diabetes (for example, diabetic polyneuropathy); polycystic ovary syndrome or compromised fertility (for example, insulin resistance hyperandrogenism and oligo-amenorrhoea); neural tube defects; CVD; neurological and psychiatric diseases (for example, bipolar depression, panic attacks and obsessive–compulsive disorders); severity of osmotic demyelination syndrome; cancers; intestinal lipodystrophy
Policosanol (++) (for example, octacosanol)	Antioxidant by reducing LDL and membrane lipid peroxidation; decreases platelet aggregation, endothelial damage and foam cell formation; vasodilatating effect; cholesterol-lowering by inhibiting cholesterol synthesis at the earliest step of the biosynthetic pathway (through down-regulating 3-hydroxy-3-methyl-glutaryl CoA reductase); lowers plasma LDL-cholesterol and increases plasma HDL-cholesterol level; affects lipid metabolism; prevents smooth muscle cell proliferation; role in cytoprotection; active energy-releasing factor; affects the nervous system (for example, anti-fatigue and improves reaction time to a visual stimulus)	CVD (for example, atherosclerosis and hypertension); gastric ulcer; athletic performances; mental health

Melatonin (+)	Antioxidant (but irreversibly oxidised), the most potent physiological scavenger of $OH^{\cdot}$: for example, reverses massive DNA degradation, stimulates glutathione peroxidase activity, increases gene expression for antioxidant or may protect against lenticular protein oxidation enzymes; effects on mood, happiness, sleep–wake period regulation and brain neuromodulation; promotes mitochondrial respiration; anti-carcinogenic, anti-proliferative and oncostatic effects through antioxidant, immunostimulating and apoptotic properties (for example, increase of natural killer cell activity as well as the stimulation of cytokine production), and also effects on gene expression; regulates the glucocorticoid receptor and blocks the activation of oestrogen receptor for DNA binding	Mental and brain health (for example, Alzheimer's disease, depression and sleep troubles); anti-ageing; cancers (for example, colorectal, breast and prostate); cataract
para-Aminobenzoic acid	Role in folate formation: for example, stimulates bacterial growth within intestines, enabling them to produce folates; cholesterol-lowering; anti-carcinogenic through down-regulation of *N*-acetyltransferase which may activate human carcinogens; acetylation in blood, notably by platelets: arachidonic acid is a main acetyl donor, suggesting the involvement of peroxisomal β-oxidation; anti-aggregatory effect: inhibits the production of thromboxane, which participates in increased arterial pressure through vasoconstriction and in blood coagulation, in human platelets; chromotrichial effect on grey hair	CVD (for example, atherosclerosis and hypertension); skin (for example, UV absorber and vitiligo) and hair health; collagen diseases; leukaemia; rheumatic fever and rickettsial diseases
Specific cereal compounds		
γ-Oryzanol in rice	Antioxidant (for example, decreases serum lipid peroxides); lowers total and LDL-cholesterol and increases HDL-cholesterol through its tocotrienol and fibre contents; improves glycaemia control through its lipoic acid content: increases glucose uptake by insulin-resistant muscle to produce energy; anti-ulcerogenic; inhibition of platelet aggregation; stimulates hypothalamus (link between nervous and endocrine system), for example, change in serum growth hormone level	Climacteric disturbances (i.e. menopausal troubles) and autonomic nervous imbalance (autonomic ataxia); type 2 diabetes; CVD; gut health (for example, gastric ulcer); mental health (for example, anxiety)
Avenanthramides in oats	Antioxidant, anti-inflammatory and anti-atherogenic: inhibit smooth muscle cell proliferation and increase NO production, inhibit aortic endothelial cell expression of adhesion molecules and their adhesion to monocytes, and reduce production of several pro-inflammatory cytokines and chemokines	Atherosclerosis
Saponins in oats‡	Antioxidant (for example, activate transcriptional activity of Cu, Zn-superoxide dismutase gene, scavenge superoxides and reduce lipid peroxidation); cause hypoglycaemia and hypoinsulinaemia; reduce non-enzymic protein glycation (i.e. HbA_{1c} level); partially reverse hypercholesterolaemia (by binding with cholesterol and impairing its absorption and/or by binding bile acids, by interfering with their enterohepatic circulation and by increasing their faecal excretion) and hypertriacylglycerolaemia; anti-fungal and anti-viral; immunostimulant and anti-carcinogenic (tumour growth suppressor and binding of primary bile acids); effects on nervous system functioning (for example, induce NO production in the brain and inhibit gap junction communication)	Colon, breast, prostate and skin cancers; CHD; skin health; nervous system health (for example, harmful stress on organs); liver health; type 2 diabetes
β-Glucans in oats and barley	Plasma cholesterol- and glucose-lowering; may indirectly affect the metabolism of bile acids (i.e. formation of secondary bile acids) and neutral sterols in intestine and liver; anti-mutagenic; anti-microbial; anti-parasitic; stimulate immune functions (for example, may stimulate proliferation and activation of peripheral blood monocytes)	Cancers; CVD; type 2 diabetes; gut health

* All data concerning physiological mechanisms and health effects are based on international references (*in vitro* studies on culture cells and *in vivo* studies in animals and human subjects; see references in Appendices).
† For these compounds, the intensity of the symbol in brackets (+, ++ or +++) refers to the importance of the compound as supplied by a predominantly cereal-based diet, based on British data collected by Truswell[19]; for other compounds, the intensity of the symbol in brackets was estimated based on the compound content in whole-grain wheat compared with other food sources.
‡ Mechanisms and health outcomes are associated with plant saponins in general, not exclusively cereal saponins.

Table 4. Whole-grain cereal bioactive compounds potentially involved in the prevention of major health outcomes and in antioxidant protection*

Major health outcome	Bioactive compound
Body-weight regulation and obesity	Insoluble fibre, fructans, resistant starch, Zn, Ca, tocotrienols, phenolic acids, flavonoids, choline, *p*-aminobenzoic acid
CVD and heart health	α-Linolenic acid, methionine, oligosaccharides, soluble fibre, resistant starch, phytic acid, Mg, Mn, Cu, Se, K, thiamin, riboflavin, nicotinic acid, pyridoxine, folates, tocopherols, tocotrienols, phylloquinone, β-carotene, lutein, zeaxanthin, phenolic acids, flavonoids, lignans, phytosterols, betaine, choline, inositols, policosanol, *p*-aminobenzoic acid, γ-oryzanol, avenanthramides, saponins
Type 2 diabetes	Soluble fibre, resistant starch, phytic acid, Mg, Zn, Se, K, Ca, tocopherols, tocotrienols, phenolic acids, flavonoids, betaine, inositols, phytosterols, γ-oryzanol, saponins
Cancers	α-Linolenic acid, oligosaccharides, soluble fibre, insoluble fibre, resistant starch, lignin, phytic acid, Zn, Mn, Cu, Se, P, Ca, riboflavin, nicotinic acid, pyridoxine, folates, tocopherols, tocotrienols, β-carotene, β-cryptoxanthin, phenolic acids, flavonoids, lignans, alkylresorcinols, betaine, choline, inositols, phytosterols, melatonin, *p*-aminobenzoic acid, saponins
Gut health	α-Linolenic acid, oligosaccharides, soluble fibre, insoluble fibre, resistant starch, riboflavin, pantothenic acid, phenolic acids, policosanol, γ-oryzanol
Mental/brain/nervous system health and neurodegenerative disorders	α-Linolenic acid, methionine, oligosaccharides, Fe, Mg, Zn, Cu, P, Ca, Na, K, thiamin, riboflavin, nicotinic acid, pantothenic acid, pyridoxine, biotin, folates, tocotrienols, phenolic acids, choline, inositols, policosanol, melatonin, γ-oryzanol, saponins
Skeleton health (i.e. bone, tendon, cartilage, collagen, articulation and teeth)	α-Linolenic acid, Fe, Mg, Zn, Mn, Cu, P, Ca, K, nicotinic acid, tocotrienols, phylloquinone, β-cryptoxanthin, flavonoids, lignans, *p*-aminobenzoic acid
Antioxidant protection (development of diseases in relation to increased oxidative stress)	Reduced glutathione, methionine, cystine, lignins, phytic acid, Mg, Fe, Zn, Mn, Cu, Se, thiamin, riboflavin, tocopherols, tocotrienols, β-carotene, lutein, zeaxanthin, β-cryptoxanthin, phenolic acids, flavonoids, lignans, alkylresorcinols, betaine, choline, policosanol, melatonin, γ-oryzanol, avenanthramides, saponins

* Prepared from data in Table 3.

a whole-grain product. The issue is still debated. The definition given by the American Food and Drug Administration[26] in 1999 was: 'For purposes of bearing the prospective claim, the notification defined 'whole grain foods' as foods that contain 51 percent of total weight or more whole grain ingredient(s) by weight' (extract). This definition was debated and contested by the European Whole Grain Task Force in 2008. They explained that: 'Using total weight gives advantage to products sold by dry weight such as crackers and ready-to-eat cereal. Because foods like breads have a proportionally high water content, even some breads made with all whole grain flours but containing significant amounts of nuts, seeds and fruit would fail to meet the 51 % by weight rule'[24]. Apparently, there is still no international consensus as to the right proportion of whole grain by dry weight (DW) in a product in order for it to be called a whole-grain product. Each country has its own definition and standards[21]. However, most research and observational studies, particularly those on breakfast cereals, estimate the whole-grain intake from products containing at least 25 % whole grains or bran by weight[5,14,27,28]. Thus, a study on young individuals aged 4–18 years found that using a 51 %-based definition underestimated the whole-grain intake by 28 %, breakfast cereals (56 %) and bread (25 %) being the major sources of whole-grain cereals[29]. In another study on adiposity among two cohorts of British adults, the same research team assumed that whole-grain foods contained ≥ 10 % whole grains and found little or no association between the whole-grain intake and anthropometric indices[30]. This suggests that the threshold of 10 % is probably too low and emphasises the need to harmonise how the whole-grain cereal food intake is calculated. In these studies, generally carried out in Western countries, whole-grain cereal foods considered are, for the most cited, whole-grain breads (for example, dark, brown, wholemeal and rye bread), whole-grain breakfast cereals (for example, muesli), popcorn, cooked porridges (oatmeal or whole wheat), wheat germ, brown rice, bran, cooked grains (for example, wheat, millet and roasted buckwheat) and other grain-based foods such as bulgur and couscous. A complete list of food ingredients classified as whole grains in the US Department of Agriculture (USDA) pyramid servings database is reported by Cleveland *et al.*[31]. Refined grain foods generally include white breads (for example, French baguette), sweet rolls, noodles, pasta, cakes, biscuits, viennoiseries, muffins, refined grain breakfast cereals, white rice, pancakes, waffles and pizza.

The importance of whole-grain cereal product consumption

There are far fewer whole-grain cereal products on the market than there are refined products, at least in Western countries. The major sources of whole-grain cereals are breads, breakfast cereals and whole-grain cereals consumed as such (for example, brown rice or quick-cooking whole-grain barley and wheat). Epidemiological data show that the consumption of two to three servings of whole-grain cereal per d is sufficient to get beneficial health effects[32]. The recommended consumption of whole-grain cereal products differs from one country to another, but most recommend increased whole-grain cereal product consumption[21,32]. For example, at least three servings daily are recommended in the USA, that is, about 48 g of whole-grain cereals[33]; between six and twelve servings daily are recommended in Australia and four servings daily in Denmark[21].

Other countries such as Canada, UK, Greece, Germany, Austria and Switzerland are not so precise and generally recommend an increase in cereal consumption with emphasis on whole-grain products[21]. Surveys carried out in the USA and the UK showed that most individuals consume less than one serving per d and about 30 % any, and that only 0·8 to 8 % of those surveyed in the USA consumed the recommended three servings per d[31,32,34]. The situation is quite different in Scandinavian countries, where individuals consume more whole-grain cereal products, particularly rye-based[32]. For example, Norwegians consume an estimated four times more whole-grain products than do Americans[35], but less than the Finns, 40 % of whom may consume four or more slices of dark bread per d[36]. Why is consumption so low in other Western countries? There are probably several reasons. First, unlike fruits and vegetables, individuals do not know about the benefits of whole-grain cereal products. Second, individuals tend to think that whole-grain cereal products are not very tasty. And third, whole-grain cereal products are less common and many are difficult to identify as being whole-grain (problem of labelling). Last, time and money have been cited as obstacles to eating more nutritiously[37].

Whole-grain and wholemeal

The terms 'whole-grain' and 'wholemeal' are mostly used synonymously. It is generally believed that whole-grain products are made with wholemeal flour, and that they may secondarily also contain intact grains. But the form in which grain is incorporated into food, intact or milled, is nutritionally significant. Thus 'wholemeal' (made of milled whole-grain flour) and 'whole-grain' (made with intact cereal grains) breads have different effects on postprandial glycaemia. The whole-grain breads produce a significantly lower glycaemic response than the wholemeal breads[38]. This underlines the importance of food structure on physiology. Thus, for clarity, the term 'whole-grain' should be used for cereal products containing more or less intact cereal kernels, and 'wholemeal' for cereal products made of more or less refined flour, in which bran, germ and endosperm are first separated, and then reassembled, in proportions that rarely correspond to those of intact grains, as the germ fraction is generally removed.

Current hypotheses and mechanisms for the protective action of whole-grain cereals

The mechanisms underlying the health benefits of whole-grain cereals are undoubtedly multi-factorial. A recent cross-sectional study on 938 healthy men and women showed that a higher consumption of whole grains, bran and germ was associated with a significant decrease in plasma homocysteine (hyperhomocysteinaemia is a risk factor for CVD) and of some markers of blood glucose control, inflammation and lipid status[17]. Other studies have linked the consumption of high-whole-grain diets with improved BMI and insulin sensitivity, lower concentrations of serum TAG, total and LDL-cholesterol and inflammation markers, and higher plasma or serum enterolactone[2,39–42]. Except for enterolactone, for which high serum levels are associated with reduced risk of CVD[43], all of the other biomarkers, when outside a normal healthy range, are all risk factors associated with the development of diabetes and CVD. There is the same kind of significant negative association between whole-grain consumption and the risk of digestive cancer[44,45]. Other mechanisms are involved in this, including the capacity of several whole-grain compounds to suppress tumour growth[46]. The next section describes the main known mechanisms by which whole-grain cereals help protect the gut and prevent the development of obesity, diabetes, CVD and cancers.

Food structure

The structure of food has long been recognised as an important parameter governing the health benefit of whole-grain cereal products. The first study was performed in 1977 by Haber *et al.* on the influence of apple structure (intact apples *v.* apple purée *v.* fibre-free apple juice) on satiety, plasma glucose and serum insulin. The removal of fibre and/or the disruption of the physical food structure was accompanied by reduced satiety, disturbed glucose homeostasis and an inappropriate insulin response[47]. Almost 10 years later, it was shown that simply swallowing carbohydrate-rich foods (rice, apple, potato and sweetcorn) without chewing was sufficient to significantly decrease postprandial glycaemia[48]. This was the simplest way to emphasise the importance of food structure (chewing *v.* no chewing) on digestion. Then, Jenkins *et al.* studied the effects of wholemeal and wholegrain breads and showed that the glycaemic index (GI) of wholemeal breads (wheat or barley flour-based) without intact grains was the same as that of white bread made of refined flour (>90), and that increasing the intact barley kernel or cracked wheat grain content of the bread (50 and 75 %) resulted in a significantly large decrease in the GI from 92–96 to 39[38]. Thus, an intact botanical food structure is more important than the composition of the food (the presence of fibre in wholemeal bread and absence from white bread) for influencing physiological responses like those related to satiety and glucose metabolism. Many later studies have confirmed these results, emphasising the importance of preserving the natural initial fibrous network, particularly in more or less intact wheat, barley, rye and oat kernels[49–52].

Whole-grain cereals as a rich source of fibre

Dietary fibre is defined by the AACC as 'the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine. Dietary fibre includes polysaccharides, oligosaccharides, lignin and associated plant substances. It promotes beneficial physiological effects including laxation and/or blood cholesterol attenuation and/or blood glucose attenuation'[53]. This definition includes that fraction of starch not digested in the small intestine, resistant starch (RS). Whole-grain wheat may contain from 9 to 17 g total fibre per 100 g edible portion (Table 2), which is more than in most vegetables (generally <6 g/100 g edible portion). Thus, consuming whole-grain cereal products is undoubtedly

a good way of increasing the fibre intake from the 10–15 g/d eaten by most Western populations to the recommended level of about 30–35 g/d.

Wheat is relatively poor in soluble fibre. It has been found that the soluble:insoluble fibre ratio is about 1:5 for whole-grain wheat, 1:10 for wheat bran and 1:3 for wheat germ (Table 2). Whole-grain wheat therefore provides large quantities of insoluble fibre (up to 11 g/100 g) and RS (up to 22 % for certain high-amylose barley varieties[54]). Cereal fibre is now recognised to be beneficial for bowel health. Wheat has a great diversity of fermentable carbohydrates. Except for lignin, whose nutritional benefits are not really known, all the types of fibre compounds, including soluble and insoluble fibre, oligosaccharides and RS, have important physiological properties and provide significant health benefits[18,55]. For example, soluble fibre increases viscosity, which delays gastric emptying and limits glucose diffusion towards the enterocytes for absorption. This leads to a lower glucose response when sufficient quantities are ingested[56].

Cereal fibres also increase satiety and help control body weight[57]. The mechanisms by which dietary fibre positively affect body weight have been previously described: briefly, they involve hormonal effects via reduction of the insulin secretion, metabolic effects via increased fat oxidation and decreased fat storage due to greater satiety, and colonic effects via SCFA production[58]. Thus, the consumption of highly viscous fibre such as β-glucans, found mainly in barley and oats, is now recommended for the management of glucose homeostasis in type 2 diabetic subjects[59]. Soluble fibre has also been shown to reduce cholesterolaemia in ileostomy subjects[60] by probably favouring an increase in bile acid excretion as shown in ileostomates following oat β-glucans consumption[61]. Increased bile acid excretion stimulates bile acid synthesis from serum cholesterol, so reducing cholesterolaemia[61].

The fermentation of fibre and RS within the colon produces SCFA that are associated with a lower risk of cancer[62,63], favouring the development of a healthy colonic microbiota (i.e. prebiotic effect)[64]. These SCFA also reduce the proliferation of human colon cancer cell lines *in vitro* [62,63]. RS is known to produce large quantities of butyrate[65]. The increased butyrate production by rats fed wheat bran is negatively associated with the proliferation of colon crypt cells that are involved in the development of colorectal cancer[66]. RS also significantly increases fat oxidation in humans, probably by increased SCFA production that inhibits glycolysis in the liver, so rendering it more dependent on fat-derived acetyl CoA as fuel, this effect being associated with a concomitant decrease in carbohydrate oxidation and fat storage[67].

In contrast, insoluble fibre, which is poorly fermented in the colon, favours an increased transit time and greater faecal bulking[68], two parameters that probably prevent colon cancer by diluting carcinogens and reducing their time in contact with epithelial cells[69]. The fermentation of some fibre also increases mineral absorption in rats, mainly by increasing the surface area available for absorption (epithelial cell hypertrophy) and/or by favouring better hydrolysis of phytic acid via enhanced fermentation, as was shown with RS[70,71] and inulin (a fructan-type compound)[72,73].

Whole-grain cereals and butyrate production

Whole-grain cereal products are an important indirect source of butyrate, produced notably through RS fermentation[65]. Butyrate has cancer-preventing properties in rats by inducing apoptosis[74] or reducing tumour mass[75]. But its positive physiological action may not be restricted to these two effects. The precise mechanisms involved in the anti-colon cancer effect of butyrate have been reviewed from *in vitro*, animal and human studies and they mainly include a combination of several physiological modifications in relation to abnormal cell growth inhibition, immune system stimulation and modulation of DNA repair and synthesis[65]. Butyrate might also protect against breast and prostate cancers, as shown by *in vitro* studies on mammary[76] and prostate[77] cancer cell lines[65]. The RS content of whole-grain cereal products depends on the proportion of the different types of RS: RS1 which is physically inaccessible to α-amylase, RS2 which is raw starch granules, and RS3 which is recrystallised/retrograded amylose that is formed when cooked food cools. It is therefore difficult to obtain precise data on the RS content of whole-grain cereal products, but some products are enriched in RS by selecting high-amylose varieties of cereal. Nevertheless, products containing whole grains or made from high-amylose cereal varieties will have proportionally higher RS contents and produce more butyrate, as was shown in human subjects fed various breads, breakfast cereals and crackers[78,79]. Whole-grain cereal products with an intact botanical structure, that is with intact kernels, will have a higher RS1 content, since it is inaccessible to α-amylase, and butyrate production. The relationship between the consumption of whole-grain cereals and/or their bran and germ fractions, butyrate production and long-term health effects deserve to be studied more thoroughly in human subjects, particularly because of the effects in rats of butyrate on fat oxidation and of total SCFA production on cholesterol synthesis reduction[80].

The 'second-meal effect'

The 'second-meal effect' is characterised by an improved carbohydrate tolerance at a meal (either lunch or breakfast, called the 'second meal') about 4–5 or 10–12 h after the consumption of a low-GI meal (i.e. the 'first meal'), an effect which may contribute to the long-term metabolic benefits of low-GI diets. It was first described by Jenkins *et al.* who used viscous guar gum[81], and thereafter for low-GI carbohydrate foods such as lentils[82]. Recently, mechanisms have been proposed to explain the sustained positive effect of low-GI whole-grain products composed of intact barley or rye kernels consumed at diner or breakfast on the glycaemic response at the following meal, breakfast or lunch[52,54,83].

The physiological mechanisms involved appear to differ according to the interval between the two meals, dinner to breakfast (about 10–12 h) or breakfast to lunch (about 4–5 h). The shorter period seems to be sufficient for the low-GI feature of the cereal product consumed at breakfast to reduce the glucose response at lunch, probably by improving blood sugar regulation and insulin sensitivity[54].

The longer interval between dinner and breakfast involved the fermentation of indigestible carbohydrates in the colon, reduced plasma NEFA and modified glucose metabolism. This indicates that the presence of specific dietary fibre (soluble or insoluble or RS) in boiled barley kernels is more significant in this 'second-meal effect' than is its low GI.

SCFA produced during the fermentation of fibre in the colon might be particularly involved[83] through at least three potential processes: a possible decrease of the gastric emptying rate by SCFA as reviewed in rats and humans[84], notably through an increased level of the polypeptide YY in blood by SCFA, that may lead to a reduced rate of glucose entry into the bloodstream; the ability of propionate and acetate to reduce serum NEFA in humans[85], circulating fatty acids being able to induce peripheral and hepatic insulin resistance in humans[86]; and, finally, the possible specific action of propionate on glucose metabolism by increasing hepatic glycolysis and decreasing hepatic glucose production as shown in isolated rat hepatocytes[87]. A later study on healthy subjects[54] confirmed that the low-GI feature of the products consumed in the evening meal was not *per se* involved in the improved glucose response at breakfast, and that the lower plasma NEFA concentration combined with the high plasma propionate content (from fermentation in the colon) contributed to the overnight benefits in terms of glucose tolerance[83]. The quantity and quality of the indigestible carbohydrates (for example, barley fibre and RS) are most important. There is also an important relationship between gut microbial metabolism and insulin resistance[54].

These results suggest that the influence of carbohydrates on glucose tolerance over a longer time (semi-acute) is optimal when the food structure is preserved (i.e. a low-GI feature) and content of RS and/or fibre is high (i.e. production of specific SCFA). Eating barley or rye kernels for breakfast resulted in lower cumulative postprandial increases in blood glucose after breakfast, lunch and dinner (a total of 9·5 h) than did a breakfast of white-wheat bread[52]. From a technological point of view, the quantity and quality of the indigestible carbohydrates is therefore particularly important, in addition to preserving a more or less intact botanical food structure, for a better control of glucose metabolism, especially to prevent type 2 diabetes.

Whole-grain cereals as rich sources of anti-carcinogenic compounds

A survey of 61 433 women found that a high consumption of whole grains (hard whole-grain rye bread, soft whole-grain bread, porridge, and cold breakfast cereals) was associated with a lower risk of colon cancer[11]. An inverse association between cereal fibre and whole-grain cereal consumption and small-intestinal cancer incidence has also been reported[12]. The roles played by dietary fibre and phyto-chemicals in preventing intestinal cancer in humans and animals have been reviewed and discussed for both human intervention and animal studies[45,69,88]. The positive action of the wheat bran oil on colon tumour incidence in rats (azoxymethane-induced cancer)[89] and mice (Min cancer model)[90] has also been demonstrated. This anti-carcinogenic effect is mainly attributed to the antioxidant and anti-inflammatory properties of several bioactive compounds, as increased oxidative stress and inflammation are involved in cancer aetiology[91]. Phenolic acids, flavonoids, carotenoids, vitamin E, *n*-3 fatty acids, lignan phyto-oestrogens, steroid saponins (found mainly in oats), phytic acid and Se are all potential suppressors of tumour growth, but human, animal and/or *in vitro* cell studies indicate that their mechanisms of action may differ (Tables 3 and 4)[46,69,92–95]. For example, cereal lignans are converted by fermentation into mammalian lignans or phyto-oestrogens (enterodiol and enterolactone). These may have a weak oestrogenic activity, and may protect against hormone-dependent cancers (prostate and breast cancers) and/or colon cancer[96]. Studies on postmenopausal women, ovariectomised rats and liver and breast cancer cell cultures indicate that phyto-oestrogens inhibit cell proliferation by competing with oestradiol for type II oestrogen binding sites[97,98]. Phytic acid would help reduce the rate of cell proliferation during the initiation and post-initiation stages (for example, decreased incidence of aberrant colon crypt foci) by complex mechanisms that involve its antioxidant properties, signal transduction pathways, gene regulation and immune response through enhancing the activity of natural killer cells[99], and its anti-carcinogenic effect seems to be dose-dependent[100]. The high phytic acid content of whole-grain cereals (up to 6 % in wheat bran) has led to questions about whether the anti-cancer activity of wheat bran should be attributed more to phytic acid than to dietary fibre[69,92]. Indeed, pure phytic acid is more efficient at reducing the incidence and multiplicity of mammary tumours in rats than is the bran fraction (All Bran; Kellogg®)[101]. The many anti-carcinogenic actions of flavonoids include their ability to inhibit various stages of tumour development in animals[102] and to reduce the mutagenicity of several dietary carcinogens in *Salmonella typhimurium* TA98NR[103]. The anti-carcinogenic activity of ferulic acid is mainly attributed to its antioxidant capacity; it scavenges the free oxidative radicals that are involved in the aetiology of cancer, and to its ability to stimulate cytoprotective enzymes[104,105]. Studies on azoxymethane-treated rats indicate that vitamin E and β-carotene inhibit the progression of aberrant crypt foci to colon cancer, especially the later stages of carcinogenesis, while wheat bran is better at inhibiting earlier stages[106]. Lignins, by hydrophobically binding bile salts, might reduce the formation of carcinogens from them[107,108]. Their adsorptive ability would increase with increased methylation of the hydroxyl moieties on the phenyl-propane units[107,108]. Lignins also reduce DNA lesions in rat testicular cells and lymphocytes both *in vitro* and *ex vivo*[109]. Se inhibits the occurrence of neoplasia in rats and mice, suggesting that an Se-poor diet is associated with an increased prevalence of neoplasia in specific human populations[110]. This probably depends on the activity of the selenoprotein glutathione peroxidase, which is involved in the development of cancers[111]. Cereal bioactive compounds act via several other anti-mutagenic and anti-carcinogenic mechanisms[112]. Important ones are the adsorption and dilution of carcinogens by insoluble dietary fibre and lignins[69,106,113,114], and the action of SCFA produced by fibre fermentation[115]. Butyrate is a major factor, as more is produced in the presence of RS, and favours apoptosis in

human cancer cell lines[62] and DNA repair in rats[116]. Interestingly, contrary to what was believed since the works of Burkitt emphasising the preponderant role of fibre in the prevention of Western diseases, notably colon cancer observed in Western countries and not in African rural population consuming high levels of dietary fibre[117], it is more and more believed today that the effect against colon cancer development might be before all attributed to RS[118], since a lower risk of colon cancer was recently observed in populations with a low level of fibre consumption but with a high intake of RS[119,120]. This reinforces the idea that specific products of RS fermentation within the colon, such as butyric acid, are the active components. Betaine[121] may be added to the list of anti-carcinogenic compounds, as its concentration can reach 0·3 % in whole-grain wheat and 1·5 % in wheat bran (Table 2).

To summarise, the anti-carcinogenic effects of insoluble fibre (including lignin), phytochemicals and wheat bran oil can be distinguished. Insoluble fibre may act directly by adsorbing or diluting carcinogens (through increased faecal bulk by water absorption), or indirectly by decreasing colon pH (through SCFA production) and increasing butyrate production. The role of phytochemicals is complex and multi-factorial, and notably involves their antioxidant properties since increased oxidative stress is a major factor in the aetiology of cancers[91,122]. The exact components of wheat bran oil that reduce the development of colon tumours are still to be identified[89,90]. However, animal experiments indicate that dietary fibre, particularly soluble fibre, may not protect against or even enhance carcinogenesis. This may be due to the abrasive property of insoluble fibre, a too low pH ($<6·5$) reached within the colon following soluble fibre and RS fermentation, the enhanced colon glucuronidase activity (that converts conjugated carcinogens to free carcinogens) and the increased production of secondary bile acids (tumour promoters) within the colon due to the increased viscosity of some soluble fibre which reduces the reabsorption of bile salt in the small intestine[123].

Whole-grain cereals as a rich source of antioxidants

Whole-grain cereals can protect the body against the increased oxidative stress that is involved and/or associated with all the major chronic diseases: metabolic syndrome[124], obesity[125,126], diabetes[127,128], cancers[91] and CVD[129,130]. Whole-grain cereals are good sources of antioxidants (thirty-one compounds or groups of compounds are listed in Table 4), as shown by measurements made *in vitro* of the antioxidant capacity of whole-grain, bran and germ fractions[131–135]. However, this may not be the same *in vivo* [136], and up to today, to my knowledge, the number of studies exploring the *in vivo* antioxidant effect of whole-grain cereals and/or their fractions in human subjects does not exceed eleven[137–147]. The antioxidants in cereals differ in their structure and mode of action[46,136]. There are indirect antioxidants, such as Fe, Zn, Cu and Se, which act as cofactors of antioxidant enzymes, and direct radical scavengers such as ferulic acid, other polyphenols (lignans, anthocyanins and alkylresorcinols), carotenoids, vitamin E and compounds specific to cereals other than wheat, such as γ-oryzanol in rice and avenanthramides in oats. These can neutralise free radicals and/or stop the chain reactions that lead to the production of oxidative radical compounds (for example, the lipid chain peroxidation stopped by vitamin E within cell membranes). Another antioxidant mechanism involves phytic acid, which can chelate Fe and thus stop the Fenton reaction producing the highly oxidative and damaging free radical $OH^{\cdot}$, ultimately reducing lipid peroxidation[148]. Lignins are also considered to be antioxidants *in vitro* (radical-scavenging activity)[149], but precisely how they act *in vivo* is not known: they may adsorb oxidative damaging compounds within the digestive tract in a way similar to bile salts adsorption[107,108]. While the action of cereal antioxidants is not well characterised once the epithelial barrier has been crossed, there is a growing belief that cereal antioxidants protect the intestinal epithelium cells from oxygen-derived free radicals[136,150], particularly those produced by bacteria that may help form active carcinogens by oxidising procarcinogens or those that may result from increased stool Fe content (Fenton reaction) due to a diet high in red meat[151]. The concept of 'dietary fibre-bound phytochemicals/phenolic compounds' was proposed recently[18,150]. The authors suggest that the antioxidant polyphenols survive digestion in the small intestine because most of them are bound to fibre (for example, esterification of phenolic acids to arabinoxylans) in the cereal food matrix. They reach the colon where the fibre is fermented and some of the antioxidants are released[150]. Vitaglione *et al.* hypothesised 'the slow and continuous release in the gut of the dietary fibre bound antioxidants', such as that of ferulic acid, which will determine the effects of these antioxidants, and considered dietary fibre to be a 'natural functional ingredient to deliver phenolic compounds into the gut'[150]. For example, only 0·5–5 % of the ferulic acid is absorbed within the small intestine, mainly the soluble free fraction[152–154], and this typical whole-grain wheat phenolic acid (about 90 % of total phenolic acids) would probably exert a major action in the protection of the colon from cancer. Thus, bound antioxidant phenolic acids might act along the whole length of the digestive tract by trapping oxidative compounds. This fraction of bound polyphenols has often led to an important underestimation of the real antioxidant capacity of whole-grain cereals – and of their fractions – as measured *in vitro* and generally based on the measurement of the easily extractable polyphenol fraction[133,155]. *In vivo* studies are now needed to examine this hypothesis, and to characterise and quantify this potential antioxidant effect within the digestive tract.

The antioxidants in whole-grain cereals act via different, complex, and synergetic mechanisms *in vivo*. However, the antioxidant action of whole-grain cereals has not yet been convincingly validated in human subjects and requires further exploration.

Whole-grain cereals as rich sources of magnesium

Among plant-based foods, whole-grain cereals, together with legumes, nuts and seeds, are one of the best sources of Mg: whole-grain wheat contains 104 mg Mg/100 g, wheat bran 515 mg, and wheat germ 245 mg (Table 2). The high Mg content of whole-grain cereals may explain its favourable impact on insulin sensitivity and diabetes risk

(Fig. 2)[156], diabetes being otherwise frequently associated with Mg deficiency[157]. Mg can increase insulin secretion and the rate of glucose clearance from the blood in humans[158,159]. This was also proposed to explain the lower insulin response in obese and overweight adults following the consumption of a whole-grain-based diet as compared with those on a refined cereal-based diet[160]. High-Mg diets reduce insulin resistance in rats fed a high-fructose diet[161]; they also reduce the development of spontaneous diabetes in obese Zucker rats, a model of non-insulin-dependent diabetes mellitus, but these rats had to be given Mg before the onset of diabetes to obtain protection[162]. Most explanations of the prevention of type 2 diabetes by Mg are based on the finding that Mg stimulates insulin-dependent glucose uptake in elderly subjects[158,163]. It also protects Mg-deficient animals from the production of reactive oxygen species[164]. Reactive oxygen species are partly responsible for the increased hyperglycaemia-mediated oxidative stress in diabetic subjects[165,166]. Mg also acts as a mild physiological Ca antagonist[167]. Obese and diabetic patients with insulin resistance have excess free intracellular Ca and these two clinical conditions are associated with hypertension[168]. In addition, Mg helps keep the concentration of intracellular Ca optimal through various complex cellular mechanisms involving Ca channels, Ca sequestration/extrusion by the endoplasmic reticulum and Ca binding sites on proteins and membranes[156]. Finally, low serum plasma Mg has been positively associated with a higher risk of coronary atherosclerosis or acute thrombosis[169], suggesting that whole-grain cereal Mg might also contribute to the prevention of CVD. This may also involve the inhibition of platelet-dependent thrombosis by Mg supplementation in patients with coronary artery disease[170] and the positive effect of Mg upon blood pressure regulation in hypertensive patients[171]. The capacity of a regular prolonged consumption of whole-grain cereals to sustain a high plasma Mg concentration therefore deserves to be investigated in the context of type 2 diabetes prevention.

The action of some anti-nutrients on starch hydrolysis and glycaemia

Whole-grain cereals are also a source of antinutrients with both adverse and positive health effects. The most important are phytic acid, lectins, tannins, saponins and inhibitors of enzymes such as proteases and α-amylases. Their main negative effect is their ability to reduce the bioavailability and the absorption of some nutrients (for example, the chelation of minerals by phytic acid and tannins), the binding of lectins to epithelial cells that damages the intestinal microvillae, and inhibition of digestive enzymes by tannins, which inhibits growth in animals[172,173]. Cereal products in the human diet are cooked; this leads to losses of antinutrients such as lectins and enzyme inhibitors, and the major health outcome appears to be the low dietary Fe bioavailability in African populations that consume sorghum or finger millet-based beverages, gruels and porridges, both cereals containing phytic acid and a high tannin content[174,175]. For example, the phytate and Fe-binding phenolic compounds in whole-grain millet flour may reach 0·6 g/100 g (DW)[176]. This is one of the key factors responsible for Fe-deficiency anaemia in developing countries[175]. On the other hand, the use of traditional processing such as germination, soaking, pre-fermentation and cooking may help to decrease the tannin and phytic acid contents, so improving Fe bioavailability[177–180].

However, phytic acid, lectins, protease inhibitors and tannins also contribute to the low-GI property of whole-grain foods[181,182]. In wheat and derived whole-grain food

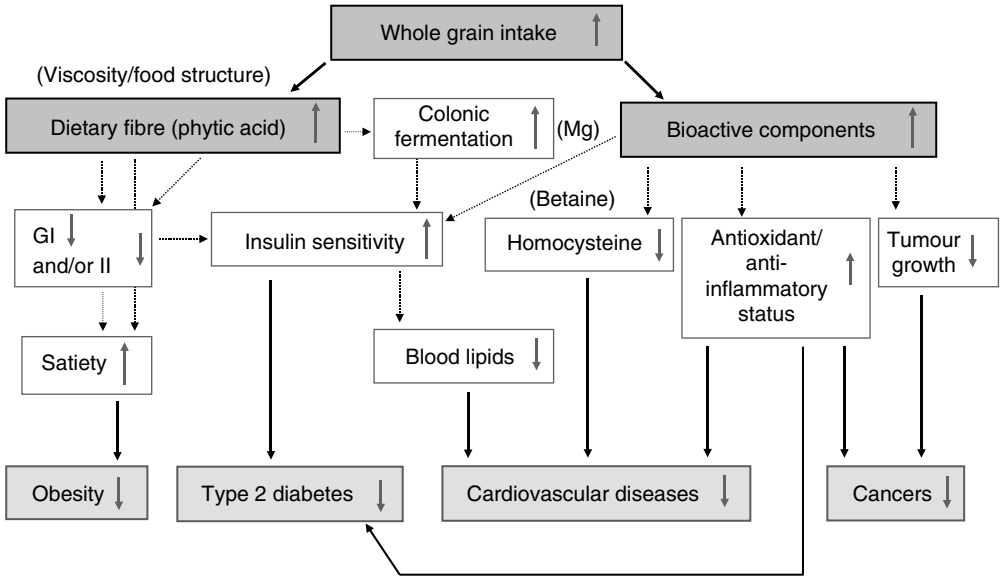

Fig. 2. Current accepted mechanisms for how whole grain protects against major chronic diseases (modified with permission from Professor I. Björck (University of Lund, Sweden); see the HealthGrain brochure for original diagram: 'Progress in HEALTHGRAIN 2008', a project from the European Community's Sixth Framework Programme, FOOD-CT-2005-514008, 2005–2010; see Poutanen *et al.*[478] for more details about the Project). GI, glycaemic index; II, insulinaemic index.

products, since lectins and enzyme inhibitors are inactivated by cooking processes, this is primarily phytic acid which would reduce glycaemia through several potential mechanisms: thus, binding with proteins closely associated with starch, association with digestive enzymes, chelation of Ca required for α-amylase activity, direct binding with starch, effect on starch gelatinisation during cooking processes and slowing of gastric emptying rate might be involved[181].

Conclusion

The proposed mechanisms by which whole-grain cereals may protect the body are shown in Fig. 2. The most important ones are the preservation of food structure, fibre fermentation in the colon, the hypoglycaemic and hypoinsulinaemic, antioxidant, anti-inflammatory and anti-carcinogenic properties of several bioactive compounds, improved insulin sensitivity by Mg and reduced hyperhomocysteinaemia by betaine, a significant CVD risk factor (for details about betaine, see the 'New hypotheses' section below). However, an extensive list of all the bioactive compounds in whole-grain wheat and its fractions (Table 2), the ways they act and their health effects as isolated free compounds (Tables 3 and 4) makes it possible to formulate new hypotheses to explain the protective role of whole-grain cereals. Whole-grain cereals, particularly wheat and/or wheat bran and germ, are also a source of *n*-3 fatty acids (especially α-linolenic acid), sulfur compounds (reduced glutathione (GSH), oxidised glutathione (GSSG), methionine and cystine), oligosaccharides (fructans, raffinose and stachyose), P, Ca, Na, K, B vitamins, flavonoids (for example, anthocyanins and isoflavonoids), alkylresorcinols, betaine, choline, phytosterols, inositols, policosanol and melatonin. The actions of these compounds will be described in the next 'New hypotheses' section. The antioxidant hypothesis will be discussed with a broader perspective, as well as the health benefits of active compounds from whole-grain cereals that are less often studied, such as B vitamins, sulfur compounds, methyl donors and lipotropes, α-linolenic acid, lignins, oligosaccharides, policosanol and melatonin.

New hypotheses: a broader perspective for the protective action of whole-grain cereals

The antioxidant hypothesis must not be reduced to free radical scavenging and antioxidant enzyme activation

There is more and more evidence that the primary effect of antioxidants from whole-grain cereals is in the digestive tract, where they protect intestinal epithelial cells from attack by free radicals[136,150]. However, the mechanisms by which antioxidants that cross the intestinal barrier protect the body remain uncertain. Published studies on animals and human subjects fed the free compounds give rise to new explanations of the antioxidant protection by whole-grain cereals. The antioxidant action of whole-grain cereals might be multi-factorial and much more complex than it first appears. There are at least four new mechanisms to be studied in the context of whole-grain cereals: the action of polyphenols on cell signalling and gene regulation modifying the redox status of tissues and cells, the action of sulfur amino acids on glutathione synthesis, the possible stimulation of endogenous antioxidants by whole-grain cereal bioactive compounds, and the underestimated antioxidant properties of phytic acid and lignin.

Whole-grain cereals as a source of polyphenols involved in cell signalling. The polyphenols in complex foods are generally not readily absorbed in the small intestine: 2–5 % for whole-grain cereal phenolic acids (Table 2), and 30–40 % for flavonoids from vegetables, beverages and fruits, depending on the food[183]. The resulting plasma concentrations of these absorbed compounds are generally in the nanomolar (nM) or micromolar (μM) range, lower than that of endogenous antioxidant compounds such as GSH and vitamin C (millimolar). However, this does not mean that they have no antioxidant action. Some quite recent studies on isolated compounds have shown that flavonoids[184,185] and phenolic acids[186,187] act on cell signalling pathways, so modifying gene regulation and/or cell redox status, as has been discussed in several recent reviews[188–191]. However, most of the studies were performed with flavonoids, not phenolic acids which are more abundant in whole-grain wheat (up to 100 mg/100 g) than are flavonoids (30–43 mg/100 g) (Table 2). Results obtained with isolated flavonoids, mainly in *in vitro* cell cultures, may be extrapolated to flavonoids found in whole-grain wheat once they have entered the bloodstream and then reached cells. Little work has been done to precisely identify wheat flavonoids. Nevertheless, some of them are catechin and proanthocyanidins[192], tricine[69], apigenin glycosides[193], and vicenin and schaftosides[194]. These flavonoids may act as signals within cells. The main mechanisms probably involve the redox status and antioxidant and pro-inflammatory genes activated by increased oxidative stress, i.e. a modified redox state of the cell, through signalling pathways that may be up- and down-regulated by polyphenols via activation or inactivation of transcription factors such as NF-κB[189,187] or activator protein-1 (AP-1)[186]. Thus, flavonoids can increase GSH synthesis through the transcription factor Nrf2 (nuclear factor-erythroid 2-related factor 2) which binds to specific antioxidant/electrophile response element (AREs/EpRE)-containing gene promoters[188]. For example, oxidised quercetin (quinone) can react with thiols in the Keap1 protein (Kelch-like ECH-associated protein 1 bound to the cytoskeleton), releasing Nrf2 and then activating specific genes via ARE/EpRE involved in GSH synthesis[188]. Here, more than the antioxidant property of the flavonoids, it is its activated or metabolised form which would be active within cells. Kaempferol and quercetin, two flavonoids, also modulate the production of γ-glutamylcysteine synthetase[195], an important enzyme in the synthesis of GSH. The authors conclude that flavonoids are important for regulating the intracellular concentration of GSH[195]. There is therefore a strong link between the intra- and/or extracellular actions of polyphenols, redox cell status and gene regulation, broadening the notion of antioxidant polyphenols to activities other than just free radical scavenging. However, most studies have used higher polyphenol concentrations (>10 μM) than those found *in vivo*. For example, the postprandial plasma ferulic acid concentrations following

wheat bran consumption in rats were about 1 μM[154] and about 0·2 μM in human subjects[196]. However, a study conducted *in vitro* on cell cultures with six wine phenolic acids in the 20 nM–20 μM range showed that ferulic, sinapic, *p*-coumaric and caffeic acids (all found in whole-grain wheat) are able to inhibit the action of pro-inflammatory transcription factor AP-1 as low as 20 nM in a range of 5–15 %[186]. Besides, it may reasonably be supposed that the true plasma polyphenol concentration is higher than the 0·2–1 μM reached with ferulic acid due to the presence of other polyphenols such as sinapic acid and, to a lesser extent flavonoids, as recently reported in human subjects where a + 5 μM increase in plasma total polyphenols has been observed 1 h after boiled wheat bran consumption[146]. Most of the sinapic acid in whole-grain wheat is free or in a soluble conjugated form (approximately equal to 70 %), and may reach a total concentration of 4–18 mg/100 g whole-grain wheat[197]. However, whether the low plasma polyphenol concentrations obtained following a whole-grain cereal meal are compatible with cell signalling activity remains to be explored.

Whole-grain cereals are a rich source of sulfur compounds. The sulfur amino acid contents (methionine and cystine) of whole-grain wheat, wheat bran and germ are 0·5, 0·6 and 1·0 % (Table 2), and may be higher in some cereal varieties (see ranges in Table 2). Methionine and cystine are both precursors of GSH, an intracellular antioxidant, and as such contribute to the control of the cell oxidative status by participating in gene expression through modification of the thiol redox status, as has been recently reviewed[198,199]. Thus, rats fed a 0·6 % free methionine diet had a higher hepatic GSH content than rats fed a control 10 % casein-based diet without methionine supplementation[200]. It has also been shown in rat gut mucosa and plasma that an inadequate intake of sulfur amino acids leads to the oxidation of the thiol/disulfide redox status (expressed by the ratios cysteine:cystine and GSH:GSSG), i.e. a less reductive potential, that in the end increases oxidative stress[201]. Methionine also generates cysteine via the cystathionine pathway[202], cysteine being oxidised to cystine (two cysteine moieties linked by a disulfide bond).

For humans, average daily intakes of 305–2770 mg methionine and 197–1561 mg cystine have been reported for a usual diet[203]. The estimated daily requirements of methionine + cysteine are 910–2100 mg/d for a 70 kg adult[204]. Based on the methionine and cystine content of commercially prepared whole-wheat bread (USDA database, 155 and 214 mg/100 g)[205] and on a daily consumption of one serving of whole-grain cereal products (i.e. about 30 g for a slice of bread)[206], whole-grain cereals provide an average 47 mg methionine and 64 mg cystine per d. This suggests that whole-grain cereals contribute little to methionine and cystine intakes, at least for low consumers. However, quite significant amounts of at least 280 mg methionine and 380 mg cystine per d can be obtained by following the USDA food guide pyramid that recommends between six and eleven daily servings of whole-grain cereal products. This would significantly contribute either to the average daily intakes as previously reported[203] or to the daily recommendations[204]. However, it is not known how a regular daily consumption of between six and eleven servings of whole-grain cereal products would contribute to GSH synthesis and/or an improved antioxidant status in humans.

GSH can be hydrolysed in the small intestine by γ-glutamyltransferase and/or absorbed intact, mainly in the upper jejunum[207]. It is therefore available to cells where it may exert its physiological effects as an antioxidant, anti-carcinogenic and/or immunostimulating[208] agent and also as detoxifier of xenobiotics. Human subjects given a solution of 46 mg GSH/kg body weight (a single oral dose of 3 g) showed no significant increase in postprandial plasma GSH[209]. Dietary GSH, but also its dietary precursors methionine and cystine, are therefore not major determinants of circulating GSH[203], probably because GSH is rapidly hydrolysed in the small intestine[209]; however, it might help detoxify reactive electrophiles in the diet within the intestinal lumen[207] or protect epithelial cells against attack by free radicals. The human daily total GSH consumption is 13–110 mg (mean 35 mg)[203]. Using the GSH highest content in whole-grain wheat (Table 2), that is about 5·7 mg/100 g, and eating 30 g whole-grain cereal per d as bread (about 38 % water), it may be calculated that whole-grain bread provides less than 1·3 mg GSH per d. Increasing the consumption of whole-grain cereal products to between six and eleven servings daily as recommended by the USDA food pyramid (epidemiological data show that an average 2·7 servings of whole-grain foods have beneficial health effects), especially servings containing wheat germ since this fraction may have 246 mg GSH/100 g – and probably more if total glutathione equivalents (GSH + (2 × GSSG) + protein-bound glutathione) are considered – might therefore provide a substantial supply of GSH. Thus, the total GSH content of high-grade extraction wheat flours (1·44–1·73 g ash/100 g) is 11·6–17·6 mg/100 g (with a water content for whole-grain wheat flour of 13·0 %), which is about three times the total GSH content of low-grade extraction wheat flours (0·54–0·59 g ash/100 g and 4·7–5·0 mg total GSH/100 g flour with an 11·9 % water content for white wheat flour), clearly showing that GSH is mainly in the bran[210]. However, a higher total glutathione content of 15·8 mg/100 g (thirty-six wheat varieties) was evaluated from data by Li *et al.* for white wheat flours[211,212]. The contribution of total whole-grain wheat GSH to the antioxidant defence, either within the gut lumen or as a substrate supplying cysteine for endogenous GSH synthesis in the liver, might be explored by comparing low-methionine and whole-grain-rich diets.

The possible action of whole-grain cereal compounds on plasma uric acid level. A recent study on human subjects consuming apples demonstrated that the elevated plasma postprandial antioxidant level (+55 μM trolox equivalents after 1 h and stabilisation at about + 20 μM trolox equivalents between 2 and 6 h; ferric-reducing ability of plasma (FRAP) assay) was due to increased uric acid and not to a significant increase in plasma vitamin C or polyphenols[213]. Fructose was thought to stimulate adenine nucleotide degradation leading to uric acid synthesis[214]. The authors proposed that the increased plasma antioxidant level following consumption of flavonoid-rich diets is due to an increase in uric acid, while sucrose, sorbitol, lactate

and/or methylxanthines are also candidates for endogenous uric acid synthesis[214]. Uric acid is a powerful antioxidant whose concentration in human plasma can reach 160–450 μM, and can account for as much as 40–90 % of the plasma antioxidant capacity[214]. A recent study on human subjects has shown that there is little or no correlation between changes in plasma total phenolic acids and antioxidant capacity (FRAP assay) following the consumption of wheat bran, indicating that compounds other than phenolic acids contribute to the postprandial increase in plasma antioxidants to about + 50 μM of FRAP between 1 and 3 h[146]. This increase is in the same range as that found by Lotito & Frei with apples[213] and with other values reported by Price *et al.* with tea, red wine, spinach and strawberries, from + 15 to + 100 μM increase in plasma FRAP[146]. This cannot be explained by the low fructose content of wheat bran (about 50 mg/100 g), much lower than that of apples (about 5·7 g/100 g)[215]. However, whole-grain cereals contain an important package of bioactive compounds other than fructose or polyphenols whose effect upon endogenous antioxidant synthesis has not been explored. It would be therefore relevant to confirm this increase in plasma antioxidant level following wheat bran consumption, and to identify the mechanisms underlying such an increase, which is apparently not due to the increase in circulating plasma polyphenols alone[146]. Work is also needed to determine whether the consumption of whole-grain cereals and/or bran and germ fractions can significantly increase the plasma uric acid concentration to those produced by coffee (+5 %) or tea (+7 %)[216].

Whole-grain cereals as a source of phytic acid and lignins. Phytic acid from whole-grain cereals has long been considered to be nutritionally negative, since it chelates minerals such as Zn, Fe, Ca and/or Mg, thus limiting their intestinal bioavailability[217]. This has been used as an argument for using refined flours instead of wholemeal wheat flours. However, phytic acid is also a strong antioxidant *in vitro*[218], and may reach 6 % in the bran of certain wheat varieties (Table 2). It therefore needs to be determined whether the negative effect of phytic acid on mineral assimilation can be offset by its antioxidant activity and the high content in minerals of whole-grain wheat. Today, the answer to this is undoubtedly 'yes'. First, the quantity of mineral chelated by phytic acid is apparently not high enough compared with the much greater quantity in whole-grain cereals compared with refined ones. Rats fed whole-wheat flour absorbed more minerals than rats fed white wheat flour[219]. Besides, baking bread according to a sourdough procedure can activate endogenous phytases and lower the pH, thus limiting the chelation of minerals by phytic acid[220]. Second, it is now known that phytic acid can chelate Fe, thus limiting the damage due to the Fenton reaction leading to the production of the very reactive free radical $OH^{\cdot}$. Third, the phytate in whole grain is accompanied by other bioactive compounds that are lost during refining. Phytic acid is therefore a serious candidate as a whole-grain cereal antioxidant acting *in vivo*. Unfortunately, I know of no studies that have explored the antioxidant effect of this compound from whole-grain cereals *in vivo*.

The concentration of lignins in whole-grain wheat is 1·9 %: 5·6 % in wheat bran and 1·5 % in germ (Table 1). Lignins are absent from refined flour and are generally considered to be nutritionally inert. However, some studies have demonstrated its potential positive physiological effects. Studies on rats showed that lignin may account for 26–32 % of the enterolactone (a mammalian lignan) formed from cereal bran[221]. Mammalian lignans are antioxidants *in vitro* at the concentrations (10–100 μM) achievable *in vivo* [222], particularly in the colon[223]. A study on rats fed a diet containing 8 % lignin for 21 d showed that lignins can have antioxidant effects on *ex vivo* fresh lymphocytes by significantly decreasing the peroxide-induced DNA strand breaks and visible light-induced oxidative DNA lesions under the form of oxidised bases via singlet oxygen – $^1O_2$ – production[224]. But I know of no studies on human subjects that have examined the physiological effects of lignins. However, if lignins are partially metabolised to mammalian lignans in humans, as they are in rats, they might add to the protection by lignans observed in human subjects against some cancers[96]. Again, studies are needed to explore the antioxidant effect of whole-grain cereal lignins *in vivo*.

Whole-grain cereals as a source of bioactive compounds with underestimated physiological effects

Whole-grain cereals as a source of lipotropes and methyl donors: betaine, choline, folates, methionine and myo-*inositol.* Betaine and choline are now recognised as important in human nutrition: betaine improves the health of the heart, liver and kidneys, while choline is important for lipid metabolism, brain development, the integrity and signalling function of cell membranes, and as a precursor of phosphatidylcholine, acetylcholine and betaine (Table 3)[225,226]. The nutritional role of folates (vitamin B_9) is also well recognised, particularly in the prevention of neural tube defects and CVD (Table 3). What is more surprising is that their contribution to the health benefits of whole-grain cereals, particularly wheat bran and wheat germ, has not been recognised until very recently (Fig. 2)[136,227]. Whole-grain wheat, wheat bran and wheat germ, respectively, contain about 0·28, 1·04 and 1·09 % betaine and choline and about 51, 231 and 420 μg folates/100 g (Tables 1 and 2). However, whole-grain cereals are not very good sources of folates as compared with legumes or vegetables, notably when based on a 100 kcal (420 kJ) content[228]. The bioavailability of choline and betaine from whole-grain cereal products and fractions is not known. However, its presence as a free soluble osmolyte[225] in cells of the aleurone layer suggests that betaine is readily available, especially compared with fibre-bound antioxidant polyphenols. To my knowledge, only two studies, using the metabonomic approach, have underlined the importance of betaine from whole-grain cereals by showing an increased hepatic, urinary and plasma betaine levels in rats and pigs fed whole-grain wheat flour and high-fibre rye bread[229,230]. This suggests that betaine from whole-grain cereals is quite available. It has also been recently shown that free betaine can reverse insulin resistance and liver injury in mice fed a high-fat diet, an animal model of non-alcoholic fatty liver disease[231]. Thus, the probably high bioavailability of

betaine from cereals[229,230] combined with its many described health effects[225] suggest that whole-grain cereal betaine may have multivariate health benefits.

Betaine, choline and folates are all methyl donors, able *per se* to transform homocysteine into methionine, thereby decreasing hyperhomocysteinaemia[232], a known risk factor for CVD[233], and also for neural tube defects[234] and cancers[235]. The dietary intake of whole-grain and bran, but not germ, is significantly and negatively associated with the plasma homocysteine concentration: −17·4 and −10·9 % when comparing the highest and lowest quintiles of whole-grain and bran cereal intake, respectively[17]. The wide variety of micronutrients may interact in synergy in this effect[17]. More precisely, one may hypothesise that folates, betaine and choline would be primarily involved. Besides, since hyperhomocysteinaemia is associated with increased oxidative stress[236,237], betaine and choline may act as indirect antioxidants.

Betaine, choline and folates are also lipotropic compounds, together with methionine and *myo*-inositol, that are essential for lipid metabolism, DNA methylation and the production of nucleoproteins and membranes[225,226,238–240]. By definition, a lipotrope is a substance that specifically prevents excess fat deposition in the liver by hastening fat removal or by limiting lipid synthesis. However, using this definition *sensu strictu*, very few studies on human subjects have been published; most have been performed on animals. It is estimated that whole-grain wheat, wheat bran and wheat germ can supply 0·51, 1·31 and 1·59 g lipotropes/100 g, respectively (Table 2). These values could be higher if other compounds with indirect lipotrope-like effects are included (those that indirectly prevent fat accumulation) such as Mg, niacin, pantothenic acid, RS, some flavonoids, PUFA, phytic acid, lignans, some oligosaccharides and fibre. Among lipotropes, as for choline, *myo*-inositol (a carbocyclic polyol) is derived from several *myo*-inositol-derived compounds that are essentially free *myo*-inositol and conjugated *myo*-inositol, either with glycosylated (for example, galactinol and di-galactosyl *myo*-inositol) or phosphorylated (for example, phytate or hexakisphosphate) groups. However, the lipotropic effect of phytate has not yet been demonstrated in human subjects and is probably low since human phytases are much less active than those in the rat small intestine[241]. In addition, among the nine isomers of inositol, only *myo*-inositol has been shown to be lipotropic, not *chiro*-inositol[242], which is abundant in the pseudo-cereal buckwheat[243,244] and is mainly known for its action against insulin resistance and its ability to help controlling blood glucose[245]. Except for *myo*-inositol phosphate (from hexakisphosphate to monophosphate) contents, there are few data on the free *myo*-inositol content of whole-grain cereals and their bran and germ fractions before processing. To my knowledge, the only published values are 86·7 mg/100 g for whole-grain amaranth[246], 8·5 mg/100 g for oats[247], 30·8–35·4 mg/100 g for whole-grain quinoa[248] and 52·5 mg/100 g for dry mature wheat embryo[249], which is quite similar to the germ fraction. The same authors also reported that dry mature wheat embryo contained about 56 mg galactinol/100 g[249]. *Myo*-inositol is therefore mainly present in phytate in cereal grains, about 95 % in wheat[250]. I have used this percentage and the phytic acid content of whole-grain wheat to estimate the free *myo*-inositol contents of whole-grain wheat, wheat bran and wheat germ (Table 2). The total *myo*-inositol content of 487 foods was published in 1980, forty-seven of which were processed cereal-based products (twenty-four types of bread, fifteen breakfast cereals and eight kinds of pasta). The total *myo*-inositol/100 g was 25–1150 mg for wheat breads and 7–35 mg/100 g for wheat-derived breakfast cereals[251]. Considering all cereal foods, the values given were then within the range 6–1150 mg/100 g for breads and 2–274 mg/100 g for other cereal foods (pasta and breakfast cereals)[251]. But these values are for total *myo*-inositol after acid hydrolysis for 40 h at 120°C, which releases *myo*-inositol from phytate in addition to free *myo*-inositol[251]. Nevertheless, hydrolysis of phytic acid within lower inositol phosphate esters (from inositol pentaphosphate to inositol monophosphate and free *myo*-inositol) by activated endogenous food phytases, through, for example, sourdough baking with natural leaven[220] and/or simple fermentation with yeast[252] and/or germination[247,252,253], may lead to free *myo*-inositol formation[247,254], as was shown by using different hydrothermal processes with lactic acid and whole barley kernels[255]. Free *myo*-inositol may then become available for absorption depending on the quantity not degraded by microflora, either during pre-fermentation or in the colon. Thus, the total free *myo*-inositol content of wheat products is difficult to ascertain precisely and probably depends on the processing parameters (which would explain the high value ranges found for breads). But it is not insignificant. Once ingested, except for folates whose bioavailability would be low when originating from cereal products, other cereal lipotropic compounds are quite readily available in the digestive tract (Table 2), *myo*-inositol being likely to be further partly converted into *chiro*-inositol after absorption, as shown in rats[256].

Wheat bran and germ are rich in choline, which is important in lipid metabolism and DNA methylation. Choline, as choline bitartrate, is often used as a lipotrope in animal diets[257], and rats fed a choline-free diet for 14 months develop severe hepatic lesions, hepatic DNA undermethylation and cellular carcinomas[258], DNA undermethylation being related to carcinogenesis development[259], as demonstrated for benign and malignant human colon neoplasms[260]. The extent to which lipotropes from whole-grain wheat such as choline help improve lipid status, by preventing fat deposition in the liver, and in balancing DNA methylation in the liver and colon deserve to be explored in prolonged trials with a whole-grain cereal-based diet. In addition to the well-known anti-carcinogenic property of several whole-grain cereal compounds (Table 4), that of choline[260] and betaine[121] should be studied more thoroughly, more particularly at the colorectal level.

The specific actions of bound and free ferulic acid. The physiological action of ferulic acid from whole grain has undoubtedly been underestimated because it is poorly absorbed by the small intestine (<5 %; Table 2), and because most studies have been conducted with the free compound at high and often unrealistic nutritional levels. These studies have nevertheless underlined the potential

role of ferulic acid as an antioxidant, anti-microbial, anti-apoptotic, anti-ageing, anti-inflammatory, neuroprotective, hypotensive, pulmonary-protective and cholesterol-lowering agent in metabolic diseases such as thrombosis, atherosclerosis, cancer and diabetes (Tables 3 and 4)[104,261,262]. However, there have been few studies on the capacity of ferulic acid from cereal products to improve some physiological functions in human subjects[104]. Ferulic acid may reach up to 0·2 % of whole-grain wheat and over 0·6 % of wheat bran (Table 2), which is quite significant; and 80 % of ferulic acid is in the bran fraction[263]. Since no more than 5 % of ferulic acid is absorbed by the intestine[153], about 95 % reaches the colon bound to fibre where it may act as a natural antioxidant on epithelial cells[150]. Thus, both free and metabolised ferulic acid (mainly sulfated and glucuronated) may have a signalling function within cells, and the bound compound might be a strong protective antioxidant and anti-inflammatory agent within the colon. The bacterial esterases in the colon will also partially and relatively slowly solubilise bound ferulic acid, as shown *in vitro* in a human model colon[264]. The possible absorption of ferulic acid within the colon and the physiological effects of its metabolites produced by the colon microbiota remain therefore to be quantified and qualified.

The specific actions of lignins. I have discussed the potential role of lignin as an antioxidant. However, lignin is one of the main non-energy-producing compounds in whole grain (about 1·9 % of whole-grain wheat, 5·6 % of wheat bran and 1·5 % of wheat germ) (Table 1). Although generally considered to be nutritionally inert, such a high concentration should have physiological effects, such as protecting the gut epithelium against oxidative damage and protecting other cell wall compounds against fermentation, so increasing faecal bulk and the associated positive health effects (dilution of carcinogens). Some studies support the hypothesis that lignins are not nutritionally inert. For example, bioactive lignophenol derivatives from bamboo lignin are anti-carcinogenic in human neuroblastoma SH-SY5Y cells, where they suppress oxidative stress-induced apoptosis[265]. It has also been shown that cell walls containing lignins (hydrophobic polymers) favour the adsorption of hydrophobic carcinogens and their release in the faeces[266]. Lignins from wheat bran also adsorb bile salts (i.e. bile salt-sequestering agent) such as deoxycholate *in vitro*, but a link between cholesterol lowering and wheat bran consumption was not demonstrated[267]. Lignin may reduce bile salt reabsorption *in vivo* by adsorbing them[268], and may further reduce the formation of carcinogenic metabolites from bile salts by colon bacteria[269]. The lignin nordihydroguairetic acid is also able to prevent changes in renal morphology, by reducing oxidative stress, in rats with diabetic nephropathy for which reactive oxygen species play an important role in its development as a result of chronic hyperglycaemia[270]. Finally, lignins from fractionated hardwood hydrolysate, when consumed during 3 weeks from an 8 % lignin-based diet, are able to decrease H_2O_2- and visible light-induced DNA damage in *ex vivo* fresh rat blood lymphocytes[224] and in testicular cells[109]. This suggests that lignin compounds or some of their metabolites have crossed the epithelial barrier, or at least have been able to induce antioxidant defences in blood by unknown mechanisms. More recently, studies using a liquid chromatography–MS-based metabonomic approach showed that lignins appear not to be metabolised by rats for 2 d, but that they probably had some effects on endogenous metabolism[271]. To summarise, lignins might act in many ways: they are metabolised to enterolactone in rats[221], their antioxidant capacity may protect the gut epithelium, they may act on endogenous metabolism, they may reduce DNA damage in blood or cells via their antioxidant capacity and they may adsorb carcinogens. All these potential physiological effects should be taken into consideration in further *in vivo* studies, especially towards cancer prevention. Lignins are therefore far from being inert and researchers in nutrition and cereal technology should ask more questions about the nutritional effects of lignins.

The combined effects of B vitamins. Whole-grain wheat, and especially its bran and germ fractions, contains almost all the B-group vitamins, vitamins B_1 (thiamin), B_2 (riboflavin), B_3 (niacin), B_5 (panthothenic acid), B_6 (pyridoxine), B_8 (biotin) and B_9 (folates). Whole wheat contains about 9·1 mg B vitamins/100 g, bran about 30·3 mg and germ about 12·3 mg (Table 1). Whole-grain cereals are particularly significant sources of thiamin, niacin, pantothenic acid and biotin compared with other food sources, and wheat germ is rich in nicotinic acid, pantothenic acid and pyridoxine. Cereal products are not a particularly rich source of folates unless fortified with folic acid (the synthetic form of folate), as it is often the case, especially for breakfast cereals. One key issue is the bioavailability of these vitamins in whole-grain cereals, but data are scarce: the few studies on the subject show that the bioavailability of each B vitamin seems to vary greatly, and that it is far from 100 % (Table 2). Thiamin and pyridoxine are the most bioavailable (Table 2). The specific action of each of these vitamins is described in Table 3. Their actions are complex and multi-factorial. The B vitamins are also called the 'B-complex vitamins' and they play an important role in maintaining muscle tone in the gastrointestinal tract and promoting the health of the nervous system, skin, hair and liver. Thiamin, nicotinic acid, pyridoxine, pantothenic acid and folates play a positive role in mental health (Tables 3 and 4). For example, folates and pyridoxine are coenzymes in the one-carbon metabolism pathways and are involved in the synthesis of serotonin and other neurotransmitters, deficits of which are implicated in deficient mental health[272]. Folates also reduce the risk of neural tube defects in babies when consumed during the periconceptional period[273]. It was recently suggested that they could be used to treat depression[274,275], as a low folate status is associated with depression[276]. Although difficult to demonstrate, it would be particularly interesting to explore the effect of whole-grain cereals on the nervous system and mental health, particularly disorders such as depression, insomnia, cognitive impairment or more generally psychic equilibrium. Other bioactive compounds, such as choline, ferulic acid, Mg, Zn, Cu, inositols, policosanol and melatonin, are also potential candidates for mental health protection and equilibrium (Tables 3 and 4).

The effects of whole-grain cereals on bone, teeth, articulation and tendon health. Whole-grain cereals and their fractions might contribute to the good health of bones, cartilages, teeth, collagen, joints and tendons (Table 3), which are all constituents of the skeleton, by the combined actions of α-linolenic acid, Fe, Zn, Mg, Mn, Cu, P, Ca, K, nicotinic acid, tocotrienols, phylloquinone (vitamin K) and β-cryptoxanthin (Table 4). While P and Ca are components of hydroxyapatite, a major constituent of bones and teeth, the Ca:P ratio in cereals, notably wheat (about 0·08; Table 2), is below the ratio of 0·5–0·8 recommended for a satisfactory Ca use by the body. Ca from whole-grain cereals is therefore unlikely to contribute significantly to the health of bones and teeth. However, the addition of calcium carbonate ($CaCO_3$) to cereal food recipes before processing might be a simple way to achieve the desirable Ca:P ratio without altering product palatability[277]. Whole-grain wheat also contains Ca absorption enhancers such as fructans and/or RS, which increase the apparent absorption of Ca from 20 to 50 % in rats[71–73]. Similarly, inulin increases Ca absorption by about 12 % in human subjects[71–73]. However, although whole-grain wheat does not contain inulin, it may contain up to 2·3 g fructans/100 g (Table 2) that might also increase Ca absorption upon fermentation. The effect of indigestible oligosaccharides such as fructans on Ca absorption and metabolism, and bone health (as measured by indices such as bone mineral content and density, and/or bone resorption rate/osteopenia) is more and more recognised today, both in rats and humans[278–280].

The results for P are less conclusive; some studies have shown increased P in bone following fructo-oligosaccharide consumption in rats[278,280], while others have found no effect[280]. P is mainly supplied by phytic acid (>85 % of the total P in grain), which has a high affinity for hydroxyapatite[281]. Indeed, the incidence of dental caries has been hypothesised to be concomitant with the change towards dietary habits of Western societies, as was shown with African Bantu acquiring susceptibility to dental decay as they adopted the European diet, through increased consumption of cariogenic refined foods such as refined sugar and white wheat bread in which a dominant caries-preventing factor would be removed during the refining process[282–284]. P, which is abundant in less refined wheat flour, is involved in this effect[285]. Thereafter, several studies on rats using organic and inorganic phosphates and different Ca:P ratios also showed the cariostatic effect of phytic acid[282,286–289], possibly through its ability to affect organic materials and the adsorption of bacteria to tooth surfaces[281], and also through its ability to be rapidly adsorbed onto hydroxyapatite, forming a natural barrier resistant to acid attacks[290] and thus to protect teeth from demineralisation and the formation of cavities by causing the desorption of salivary proteins from hydroxyapatite, the first step in plaque formation[281,291]. But, later, Cole & Bowen failed to show a significant effect of feeding monkeys with phytic acid for 2 weeks on the physical properties of plaques (such as dry and wet weights), or their chemical properties (protein, carbohydrate, Ca, Mg and P contents), or the microbial composition[292]. Further studies in human subjects are therefore needed to ascertain the cariostatic role of phytic acid, and perhaps of other cereal bioactive compounds, in subjects on a regular whole-grain cereal diet.

Whole-grain wheat also contains mammalian lignans (0·2–0·6 mg/100 g; Table 2) that seem to protect against osteoporosis (Table 3), notably in the postmenopausal period. Japanese women consuming high concentrations of phyto-oestrogens were found to have fewer hip fractures than women in the USA or Europe[293]. However, the effect of lignans on bone health remains to be confirmed. To my knowledge, no research has answered this particular issue of the role of long-term whole-grain cereal consumption on skeletal health and bone physiology.

Whole-grain cereals as a source of oligosaccharides. It has previously been seen that whole-grain cereals are rich in fibre (including RS) and oligosaccharides that may have both a prebiotic effect by favouring the development of a healthy microbiota[294,295] and that enhance mineral absorption through hypertrophy of the gut epithelium[70,71]. Thus, whole-grain wheat contains 1·9 %, its bran has 3·7 % and the germ fraction 10·1 % of fructans (fructo-oligosaccharide), raffinose and stachyose (Table 1). The average wheat germ raffinose content is about 8 % and may reach 10·9 %, which is quite high (Table 2). Whole-grain wheat contains about 0·4 % of raffinose and wheat bran has 1·2 % (Table 2). The stachyose content is lower: 0·1 % in whole-grain wheat, 0·2 % in wheat bran and no data are available for wheat germ (Table 2). Raffinose is a trisaccharide composed of galactose, glucose and fructose. Stachyose is a tetrasaccharide formed with two galactose molecules, one glucose and one fructose. To my knowledge, there are no published data on the health effects of these whole-grain cereal oligosaccharides, apart from the fact that they are both considered to reinforce the fibre effect of whole-grain cereals, by producing SCFA generally favourable to large-bowel health. They are completely fermented *in vitro* within 48 h in the presence of a piglet faecal inoculum[296]. Rats fed a 3 % raffinose-based diet for 21 d have a significantly reduced weight gain, more lactobacilli and fewer streptococci, greater SCFA production, and, interestingly, a lower plasma TAG concentration with no effect on plasma cholesterol[297]. However, it must be noted that fermented products (notably breads) constitute an important part of the whole-grain cereal food consumption of humans; and fermentation may lead to the partial breakdown of fructans, raffinose and stachyose by bacteria.

The specific action of phytosterol and of little studied bioactive whole-grain cereal compounds: α-linolenic acid, policosanol, melatonin and para*-aminobenzoic acid.* The concentration of α-linolenic acid, an *n*-3 fatty acid (18 : 3) with many positive health effects (Table 3), may reach 0·5 % of wheat germ and almost 0·2 % of wheat bran (Table 1). A diet containing about 2·7 g α-linolenic acid-rich wheat germ oil per d has an anti-atherosclerotic effect in mildly hypercholesterolaemic subjects; it acts by inhibiting oxidative stress-mediated synthesis of CD40L (protein involved in the progression of atherosclerosis with inflammatory and prothrombotic properties)[298]. Wheat

germ contains 0·53 % α-linolenic acid, so one should consume about 500 g/d to reach the 2·7 g tested in the present study, which is not really realistic. However, a regular consumption of wheat germ as a nutritional complement and/or of wheat germ oil is nutritionally relevant.

Phytosterols, policosanol and melatonin, although present at lower concentrations, also possess numerous positive health effects (Table 3). Phytosterols, known for their cholesterol-lowering effect in humans[299,300], are particularly high in wheat germ (430 mg/100 g) (Table 2) but their health effects are not known when they come from whole-grain cereals. Policosanol is a natural mixture of high-molecular-weight aliphatic primary alcohols (C24 to C34) in which octacosanol is the main compound[301,302]. Although less nutritionally studied, policosanol is also a lipid-lowering agent (for example, total and LDL-cholesterol) in both human subjects and animals at levels of about 10–20 mg daily, and it can also increase HDL-cholesterol up to + 30 %[303,304], making it a promising agent in CVD prevention and treatment[304]. Whole-grain wheat contains about 3 mg policosanol/100 g (Table 2). One recent study has shown that eating chocolate pellets supplemented with wheat germ policosanol (20 mg/d) for 4 weeks does not reduce blood cholesterol or modify the blood lipid profile of healthy human subjects[305]. A diet containing about 100 mg policosanol/d eaten for 30 d reduced the increase in plasma LDL-cholesterol in hypercholesterolaemic rabbits by reducing cholesterol synthesis in the liver through increased LDL catabolism[306]. Feeding policosanol to rats for up to 4 weeks (250 and 500 mg/kg per d) significantly renders the lipoprotein fractions (VLVL + LDL) resistant to *ex vivo* Cu-mediated oxidation[307]. In view of these results, the policosanol content of whole-grain wheat seems too low (about 3 mg/100 g) to significantly improve the blood lipid profile in humans. Rather, it is probably the combined action of the different cholesterol-lowering compounds of wheat (for example, SCFA produced by undigestible carbohydrates, soluble fibre, tocotrienols, phytosterols and policosanol) that contributes to improve the blood lipid profile to its optimum.

The concentration of the mammalian pineal hormone melatonin, which can be extracted from numerous plants, is about 0·3 μg/100 g in whole-grain wheat (Table 2)[308]. This compound has a positive effect on human mood, cognitive functions, prolonged sleep period and brain neuromodulation[309,310], but it may also be an antioxidant[310] and anti-carcinogen[311,312] (Table 3). The health effects of melatonin in humans when originating from whole-grain cereals are not known: as for policosanol and other cholesterol-lowering compounds, due to the low melatonin content of whole-grain wheat (Table 4), this is probably the combined action of melatonin and of other compounds acting positively on mental and brain health that has to be considered first.

Para-aminobenzoic acid has also been detected in cereals. Values are scarce and not recent: reported values are 0·34–0·55, 1·34 and 0·852 mg/100 g for whole-grain wheat, bran and germ fractions, respectively[313,314]. *Para*-aminobenzoic acid is best known as a sunscreen agent that protects the skin from UV radiation[315], but it also stimulates bacterial growth in the intestine and is an intermediate in the bacterial synthesis of folates. Besides its role in folate formation, *para*-aminobenzoic acid has long been used to treat rickettsial infections and may lead to a 11·5 % decrease in serum cholesterol in man, when consumed at 8 mg/d in the form of its Na salt[316,317]. *Para*-aminobenzoic acid down-regulates *N*-acetyltransferase in human cell cultures (peripheral blood mononuclear cells)[318] – acetylation plays an important role in the activation of several potential human carcinogens[319,320], and inhibits the production of thromboxane which participates in blood coagulation (anti-aggregatory effect) and in increased arterial pressure through vasoconstriction[321]. However, these studies used *para*-aminobenzoic acid concentrations of 30–100 μM, about 4–137 mg/l, which is far higher than the quantity that can be obtained from eating whole-grain cereal products, as whole-grain wheat containing only 0·34–0·55 mg *para*-aminobenzoic acid/100 g (Table 2). Thus, like the other bioactive compounds present at low concentrations in whole-grain wheat (for example, policosanol and melatonin), the health benefit of cereal *para*-aminobenzoic acid has to be considered complementary to that of other cholesterol-lowering, anti-carcinogenic and anti-aggregatory compounds.

The nutrigenomic approach

Nutrigenomics in nutrition is devoted to the study of the influence of dietary interventions on gene transcription (transcriptome), protein synthesis (proteome) and metabolites (metabolome, the whole set of metabolites) in cells, body fluids and tissues[322–326]. One of the most important objectives of nutrigenomics is to detect and identify early metabolic disturbances and their regulation (for example, in relation to oxidative stress or inflammation) that can lead to more serious chronic diseases. The possibility of detecting some diseases early could change clinical nutrition and public health practices[326]. This implies studying the effects of bioactive compounds in whole-grain cereals on gene expression, protein synthesis and the metabolome. In the field of nutritional studies, besides the measurement of usual biomarkers such as plasma glucose (for example, GI) or urinary lipid peroxides (oxidative stress index), it seems particularly important to focus on the metabolome, which reflects both the endproducts of metabolism and the changes over time of metabolism following food consumption. While many metabolomic studies have been done with isolated compounds, notably in pharmacology for drug toxicity[327], very few have been done with complex food products. In metabolomics and nutrition, only a few studies have been performed[328]: to characterise the metabolic effect of energy restriction[329], vitamin deficiency[330] or of intake of PUFA-rich oils[331], antioxidant-rich foods such as soya[332], chamomile[333] and tea[334], or of pure dietary antioxidants such as epicatechin[335], catechin[336] or ferulic and sinapic acids and lignins[271]. Studies on rats have been carried out using the metabolomic approach to explore the metabolic fate and the effect on endogenous metabolism of whole-grain and refined wheat flours[230] and of lignin-enriched wheat bran lignins[271]. It has thus been shown that whole-grain wheat flour consumption leads to significant increases in liver betaine and GSH and decreases in some

liver lipids, but has no effect on conventional lipid and oxidative stress biomarkers. It also causes a greater urinary excretion of tricarboxylic acid cycle intermediates, aromatic amino acids and hippurate (from phenolic acid degradation in the colon). When the diet was changed to refined wheat flour, a new metabolic balance was reached within 48 h, and conversely from refined to whole-grain flour (Fig. 3)[230]. The metabolomic approach also showed that rats did not appear to metabolise lignins from wheat bran within 2 d of the regimen, but they are likely to affect endogenous metabolism through mechanisms which need to be elucidated[271]. Results are convincing in that new metabolic effects have been unravelled using this new open approach, for example, the role of symbiotic microbiota in triggering diet-induced mechanisms of steatosis[337] or some specific metabolic pathway disturbances in diabetic rats[338], thus improving our understanding of diseases and the mechanisms responsible for them. However, more significant conclusions could be drawn once the databases for compound identification are completed and distributed. To my knowledge, few if any studies have investigated the effect of consuming complex whole-grain cereals and their fractions on gene expression. The tools are now available to study this, which would provide important information about which gene-regulated metabolic pathways are stimulated by the synergetic action of the bioactive compounds in whole-grain cereals, not the restricted action of isolated compounds. Thus, nutrigenomics should enable us to better characterise the metabolic pathways affected *in vivo* by the antioxidants in whole-grain cereals.

Conclusion

The metabolic fate and health effects of major compounds such as lignin (up to 9 % in wheat bran), ferulic acid (up to 0·6 % in wheat bran), phytic acid (up to 6 % in wheat bran) and betaine (up to 1·5 % in wheat bran) (Table 2) have been little studied when originating from whole-grain cereals. Yet, these three compounds may account for about 11 % of wheat bran (Table 1), and therefore deserve to be studied more. Wheat germ also merits greater attention since it contains quite significant levels of bioactive compounds such as α-linolenic acid (about 530 mg/100 g), GSH (about 133 mg/100 g), GSSG (about 69 mg/100 g), thiamin (about 1·75 mg/100 g), vitamin E (about 27·1 mg total tocols/100 g), flavonoids (about 300 mg/100 g), betaine (about 851 mg/100 g), choline (about 223 mg/100 g), *myo*-inositol (> 11 mg/100 g) and phytosterols (about 430 mg/100 g) (Table 2). It thus contains 2·5 % of vitamins and minerals, at least 1·6 % of lipotropic compounds and 1·2 % of sulfur compounds. All these compounds are involved in the new hypotheses proposed here and their corresponding physiological mechanisms. Based on past and new hypotheses, a synthetic view of the mechanisms underlying the health benefits of whole-grain cereals and their fractions can be proposed (Fig. 4). The diagram purposefully illustrates the complexity of the mechanisms involved and their obvious synergy and interconnection *in vivo*. Due to this complexity, whole-grain cereal bioactive compounds are listed in Table 4, ranking according to the five major health outcomes generally considered in the literature: body-weight regulation, CVD, diabetes, cancers, and gut health; mental, brain

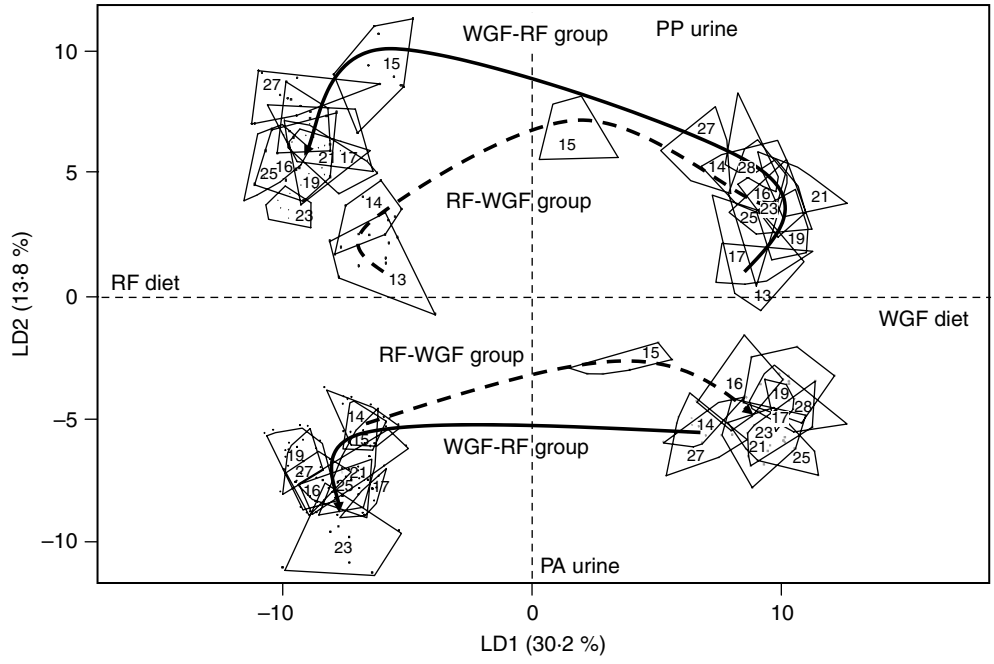

Fig. 3. Linear discriminant (LD) analysis score plot of the ^{1}H NMR urinary spectra highlighting the separation before, between and after the diet change (days 14−15) and between the urine sampling times (postprandial (PP) and post-absorptive (PA)). (- - - -), Refined flour followed by whole-grain flour consumption (RF-WGF) group; (—), whole-grain flour followed by refined flour consumption (WGF-RF) group. Each polygon represents the limits of the metabolic profile obtained for the ten rats of a given group at a given day and urine sampling time. Urine samples were collected from days 13 to 28 (for details, see Fardet *et al.* [230]).

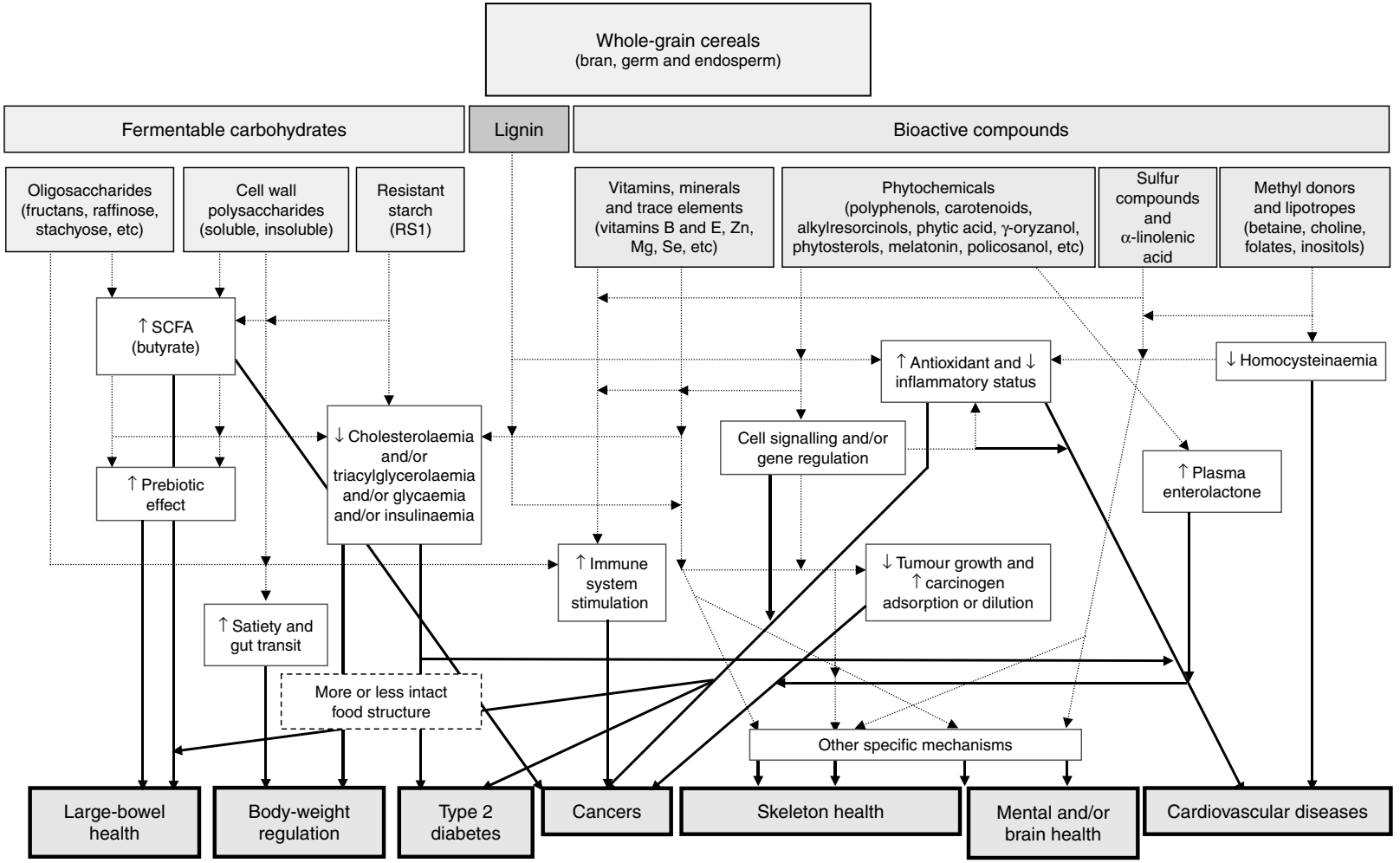

Fig. 4. Current and new proposed physiological mechanisms involved in protection by whole-grain cereals (adapted from Table 3). The dotted thin arrows (····>) indicate the link between whole-grain bioactive compounds and protective physiological mechanisms, while the plain arrows (→) indicate the relationship between physiological mechanisms and health outcomes.

and skeleton health being new proposed ways to explore. One important question remains: do bioactive compounds exert the same effects when they are free compounds and when they are in whole-grain cereals? This is notable, because their bioavailability in whole-grain cereals is probably lower than the free compounds (Table 2) and because the quantities in whole-grain cereal products do not match the daily human needs. Again, it is probably the summed and combined action of all the bioactive compounds on a particular physiological function (as illustrated in Fig. 4 and Table 4) which leads to improved specific physiological functions such as antioxidant status and glucose homeostasis, especially when whole-grain products are consumed daily, generating long-term health benefits. This is why it is urgent to carry out further *in vivo* studies both in rats and human subjects, to unravel the complex mechanisms activated by the consumption of highly complex foods such as whole-grain cereal products. Intervention studies on human subjects consuming whole-grain cereals are so rare that they should be carried out first. The non-invasive characteristic and high potential of the metabolomic approach for unravelling new metabolites and metabolic pathways affected by a given diet and its ability to explore the complexity inherent in metabolism means that it should accompany the measurement of the usual biomarkers in order to describe the metabolic actions of whole-grain cereals in all their complexity. The mechanisms described in Fig. 4 are complex, but are above all interconnected as in the whole organism. Metabolomics therefore seems to be the most appropriate tool for studying such an interconnectedness, and so provide a more realistic view of how whole-grain cereal bioactive compounds act in synergy. For example, inflammation, oxidative stress and immune system-related metabolic pathways are generally all involved in cancers, as is the case for other metabolic diseases in which there is a progressive metabolic imbalance following an unhealthy diet. Finally, genomic studies are needed on the action of whole-grain cereals on gene regulation, as bioactive compounds really exert their physiological effects within the cell. While isolated free bioactive compounds may be used for *in vitro* studies on cell cultures, studies in animals and human subjects should use an integrated 'complex food approach'.

Cereals other than wheat

The present review discusses whole-grain wheat, since it is one of the most widely consumed cereals, especially in Western Europe. However, most of the bioactive compounds in wheat are also present in other major cereals such as rice, maize, oats, barley, sorghum and millet. The main differences lie in the relative contents of each of these compounds, their distribution in bran, germ and endosperm and the proportions of the bran and germ fractions. Nevertheless, compounds such as γ-oryzanol, avenanthramides and saponins are specific to cereals other than wheat.

The bran fraction

The proportion of the bran fraction varies with the cereal type: for wheat, rice and maize, it is 10–16 % of the whole grain. The bran fraction in rice contains about 15–20 % oil[215,339]. This oil is rich in bioactive compounds and contains more than 100 different antioxidants, such as lipoic acid, a powerful antioxidant[340,341] that helps prevent cognitive deficits, is beneficial in the treatment of Alzheimer's disease[342], and may protect against risk factors of CVD[343]. Rice bran contains tocotrienols (10·6 mg/100 g)[344], γ-oryzanol (281 mg/100 g)[344] and up to 1·2 % phytosterols[345] such as β-sitosterol, all of which may help improve the blood lipid profile and reduce the risk of CVD[346–348]. Rice bran also contains up to 21 % dietary fibres[345]. Maize bran has more dietary fibre than wheat and rice bran, about 74–79 %[215,349,350]. It contains about 4 % phenolic acids, about 50 % heteroxylans and about 20 % cellulose, and is almost devoid of lignins[350]. It is particularly rich in ferulic acid (up to 3 %), mainly in a very resistant (to enzymes) bound form[351]. And, contrary to wheat for which phytate is essentially in the bran fraction, 90 % of maize phytate is in the germ fraction[352].

Some specific compounds

Some bioactive compounds are quite specific to certain cereals: γ-oryzanol in rice, avenanthramides and saponins in oats, and, although present in other cereals such as wheat, β(1 → 3)(1 → 4)-glucans in oats and barley, and alkylresorcinols in rye. Their mechanisms of action and health effects are shown in Table 3.

γ-Oryzanol in rice. γ-Oryzanol is derived from rice bran oil and is a mixture of substances including sterols and ferulic acid, and at least ten phytosteryl ferulates (for example, methylsterols esterified to ferulic acid). Its content in whole-grain rice is 18–63 mg/100 g (DW)[339,353] and in rice bran 185–421 mg/100 g, depending on the rice variety, milling time, stabilisation process and extraction methods[344,354–356]. Its antioxidant activity has been demonstrated *in vitro*[357]. Its health effects are diversified, with positive actions against CVD and hyperlipidaemia, as shown in animal models through cholesterol-lowering, lipid peroxidation reduction and anti-atherogenic effects[348,358–360] and in human subjects[361].

Avenanthramides and saponins in oats. Aventhramides are specific polyphenols from oats. They are substituted cinnamic acid amides of anthranilic acids and there are at least twenty-five distinct entities[362]. Total avenanthramide content in five oat cultivars (husked and naked) ranges from 4·2 to 9·1 mg/100 g[363], while the oat grain contains 4–13 mg avenanthramide 1/100 g (the major avenanthramide), again depending on the oat cultivar[364]. The avenanthramide content in oat bran is 1·3–12·5 mg/100 g according to the type of avenanthramide considered[364,365]. As polyphenols, they are strong antioxidants both *in vitro*[366,367] and *in vivo*[140]. They play a particular role in the prevention of CVD due to their anti-inflammatory and anti-atherogenic effects[368], and by protecting LDL from oxidation, in synergy with vitamin C, as shown on human LDL[369].

Saponins are glycosides with a steroid or triterpenoid aglycone[370]. They are especially found in oats, which synthesise two families of saponins, the steroidal

avenacosides and the triterpenoid avenacins[371]. The saponin content, depending on the oat cultivar, seems to be situated mainly within the endosperm and has been shown to vary from 0·02 to 0·13 % (DW)[372,373]. Saponins have a wide range of biological activities (about fifty are listed by Güçlü-Üstündag & Mazza[370]), such as anti-carcinogenic and hypocholesterolaemic[374], stimulation of the immune system[375,376] and cholesterol-lowering[377]. However, it is not known whether all these properties could be ascribed to cereal saponins. Saponins are also poorly absorbed by the gut[267].

β(1 → 3)(1 → 4)-Glucan in barley and oats. The β(1 → 3)(1 → 4)-glucan content of oats and barley is especially high. Total, insoluble and soluble barley β-glucan contents vary widely with the variety, the presence of hull (i.e. hulled *v.* hull-less) and the amylose content[378]. Thus, the water-soluble β-glucan content of barley is 0·5–8·3 % (w/w, DW)[378–385], the insoluble fraction is 1·2–21·7 % (w/w, DW)[379–381] and the total β-glucan content is 3·0–27·17 % (w/w, DW)[379–381,383]. Total β-glucans contents vary widely and might be attributable, in addition to variety variability, to the method of extraction and possible confusion in some studies where the soluble β-glucan fraction seems to be confounded with the total β-glucans.

The soluble β-glucans content of naked oat grains is 3·9–7·5 %, and in hulled oat grains it is 2·0–7·5 % (w/w, DW); the insoluble content of naked oat grains is 5·2–10·8 % and that of hulled oat grains is 13·8–33·7 % (w/w, DW)[381,386]. Much work has already been done on the health effects of β-glucans, particularly their glycaemia- and cholesterol-lowering properties, having implications for type 2 diabetes[387] and CVD[56,388,389]. As soluble viscous fibre[383], they slow the rate of gastric emptying, and the diffusion of glucose and NEFA into epithelial cells for absorption in both animals and humans[56,389]. However, a recent study conducted on healthy subjects demonstrated that muesli enriched with oat β-glucans had no more effect on gastric emptying rate than did cornflake-based muesli, despite its plasma glucose-lowering effect[390]. β-Glucans are also positively involved in the protection against cancers, especially through reactions with mutagenic agents to prevent them interacting with DNA as shown in rodent and human cell lines[391].

Alkylresorcinols in rye. Alkylresorcinols are plant-derived phenolic lipids, especially found in whole-grain cereals. Rye contains the highest concentration of alkylresorcinols, which can be twice that of wheat (up to 320 mg/100 g DW)[392]. They are 1,3-dihydroxybenzene derivatives with an alkyl chain at position 5 of the benzene ring, which gives them an amphiphilic feature. They are apparently relatively well absorbed within the small intestine (about 58 %; Table 2) of ileostomates following the consumption of soft bread enriched with rye bran and whole-grain rye crispbread[393], making them (either intact in plasma or as metabolites in urine) potential biomarkers of whole-grain rye and wheat intake[394–396], especially for epidemiological research and observational studies[396,397]. Their biological activity is multifactorial[396], from interacting with metabolic enzymes (for example, inhibiting 3-phosphoglycerate dehydrogenase, the key enzyme in TAG synthesis in adipocytes)[398] to decreasing cholesterol in the rat liver[399], to anticancer/cytotoxic effects but almost exclusively *in vitro* [400,401].

New bases for improving the nutritional properties of cereal products

The elucidation of the mechanisms by which whole-grain cereals protect our bodies, together with a better understanding of how bioactive compounds are released from the cereal food matrix and delivered to the bloodstream, will provide important information for the industrial development of cereal products with improved nutritional qualities. Surprisingly, the present supply of cereal products of a good nutritional quality is still limited. I believe that the best way to improve the nutritional quality of cereal products is to combine the preservation of a relatively intact botanical food structure (as far as the recipe allows it), a low-GI feature and a high nutritional density of fibre and bioactive compounds, by using less refined flour with a higher extraction rate. These factors are important but probably not sufficient to ensure that the right macro- or micronutrient reaches the right site of absorption for an optimal physiological effect. This is why more and more private and public research is aimed at modelling the fate of nutrients from complex foods within the intestine so as to predict their bioaccessibility and thus control their delivery for a specific physiological effect[402–404].

Optimising and controlling the delivery of bioactive compounds for improving health

There are great differences between the food content in a defined nutrient and the percentage really metabolised, or even absorbed. This is especially true for cereal products where numerous factors linked to the food matrix may limit the release of macro- and micronutrients. There is increasing evidence that the physical structure of natural cereal food matrices (for example, intact cereal kernels) or the artificial microstructure of processed cereal products may either favour or limit the bioavailability of nutrients, and thus their nutritional effects. However, differences in bioaccessibility–bioavailability of nutrients, particularly micronutrients, at present cannot be correlated with differences in long-term health effects, except for the positive health effects of starch and its so-called slowly digestible fraction[405,406]. The question is therefore: is there a positive correlation between increased or decreased bioaccessibility of a given nutrient and its health effect? This probably depends on the nutrient considered and on the health status of the subject. For example, the rapid release of glucose from starch digestion into the bloodstream is advantageous in some situations (for example, the urgent need for glucose for brain or muscles to function, as for immediate intellectual and physical efforts), and harmful in other situations (for example, type 2 diabetes). The same approach is now being developed for proteins (slow *v.* rapid proteins) and lipids for which their physical state and/or their physico-chemical properties may influence the release of amino acids and fatty acids, respectively, into the bloodstream. The resulting significant metabolic impact

could be used in some situations such as diabetic subjects[407], the elderly[408] and for patients on enteral nutrition suffering from pancreatic insufficiency to adequately hydrolyse lipids[409].

In vitro bioaccessibility and *in vivo* bioavailability studies with vegetables and whole-grain cereals and/or their fractions have clearly shown that food structure affects the bioavailability of polyphenols, carotenoids, minerals, trace elements and vitamins (Table 2)[403]. Table 2 shows the results of bioavailability studies on whole-grain wheat products and wheat bran. Much data are still lacking: studies exploring the bioavailability of compounds in whole-grain cereals are scarce and the products are often consumed as part of a complex diet that also supplies the same bioactive compounds from other foods. For example, studies on mineral or trace element bioavailability in rats often included mineral mixtures that made it difficult to determine the exact apparent absorption of the mineral supplied by the cereals. Thus, radiolabelled cereal products should be used more frequently to answer such questions. The few data obtained show that bioactive compounds are far from being 100 % bioavailable within the small intestine. No more than 5 % of the ferulic acid in wheat bran is released into the small intestine, so that most reaches the colon where it can exert an antioxidant protective action on the gut epithelium. On the other hand, there is convincing evidence that the small proportion absorbed in the small intestine can affect cell signalling and the activation or repression of some genes. Thus, in a way similarly to starch, it seems that two fractions of ferulic acid can be defined: the rapidly available ferulic acid released and absorbed in the small intestine (i.e. free and soluble-conjugated), and slowly available ferulic acid gradually released mainly in the colon (i.e. ester-linked)[264], each fraction having its own health benefits.

Betaine (about 0·9 % of wheat bran; Table 1), unlike ferulic acid, is probably much more bioavailable since it is not bound to other constituents: is there a need to slow down its release and to favour a fraction reaching the colon, for example, for improving its anticancer effect[410]? The same issue, that is the optimal bioavailability to reach, might be questioned for polyphenols such as lignans and alkylresorcinols, vitamins and minerals, and phytosterols. The problem for phytic acid is slightly different; we need to know the extent to which it is reasonable to pre-hydrolyse it in order to combine a maximum mineral bioavailability with its antioxidant effect in the gut against free radicals produced by microbiota, and from its potential hypoglycaemic effect as well.

Otherwise, the case of fibre is not yet resolved for whole-grain wheat which contains more insoluble fibre than soluble fibre (soluble:total fibre ratio is about 0·16; calculated from Table 2): what would be the optimum ratio of soluble:total fibre to reach? It is not known to what extent it would be beneficial to increase the soluble fibre content, for example, by pre-hydrolysing insoluble arabinoxylans to soluble arabinoxylans (soluble:total arabinoxylans ratio is about 0·18; calculated from Table 2). Soluble fibres may be beneficial to health by reducing the postprandial glucose response through increased viscosity[411] (see Tables 3 and 4), but they may also be harmful, by, for example, increasing the risk of colon cancer[412].

Provided it has positive health benefits, the range by which industrial processes can improve the bioaccessibility and bioavailability of cereal bioactive compounds is therefore large. This approach has been applied to starch with success[413], by controlling its delivery in the gut by rendering it more slowly hydrolysed (i.e. slowly digestible starch) within the small intestine, or by making it inaccessible to α-amylase (i.e. RS), so that a fraction of starch reaches the colon where it is fermented to the anti-carcinogenic molecule butyrate, the preferred fuel for colonocytes (see Whole-grain cereals and butyrate production section). Technologists know how to modulate the proportions of these three fractions in cereal products, i.e. rapidly, slowly and indigestible starch. RS is representative of the different ways it can be used by breeders and technologists to control the delivering of a compound, i.e. starch, within the digestive tract. It has been seen that the RS content of whole-grain products may be very high, up to 12 % in ordinary barley kernels and even 22 % by combining intact botanical structure with a high-amylose barley variety[54]. The formation of RS can be technologically favoured through starch encapsulation within the cereal food matrix by protein or fibre networks (RS1), restricting starch granule gelatinisation (RS2), the use of high-amylose cereal varieties with a high content of retrograded starch (RS3) and/or chemical modification such as acylation (RS4). RS is now considered to be a prebiotic compound that can positively modify microbiota growth in quality and quantity within the colon[414,415]. If technologists may be able to modify processing parameters such as temperature, extrusion pressure, retrogradation and/or chemical modification to increase the RS content, breeders can select high-amylose cereal varieties[294,416], amylose being more slowly digested than amylopectin[417,418].

The traditional use of fermentation and the development of new technologies

Fig. 5 shows the ways in which the nutritional quality of whole-grain cereals can be improved. There are mainly three: the growing conditions, the genetic approach and through technological processes.

Growing conditions. The growing conditions, for example, the use of adequate fertilisers, can increase the cereal content of Se, Mg, Fe and Zn[419–421] with possible modified physiological effects in humans[422]. An increase in environmental stress, for example, water stress, cold or exposure to micro-organisms, may favour the synthesis of antioxidants by the plant to combat this stress. This has been shown with α-tocopherols, carotenoids and betaine in wheat seedlings and sugarbeet roots under temperature- and salt-stressed environments[423,424].

Genetic approach. The genetic approach[425] using conventional tools (indirect action on genes) such as cross-breeding and hybridisation to combine varieties high in some bioactive compounds, for example, Zn, Fe and pro-vitamin A[426,427], and/or low in others, for example, phytic acid[428,429], and non-conventional tools (direct action on genes) such as genetic engineering to modify

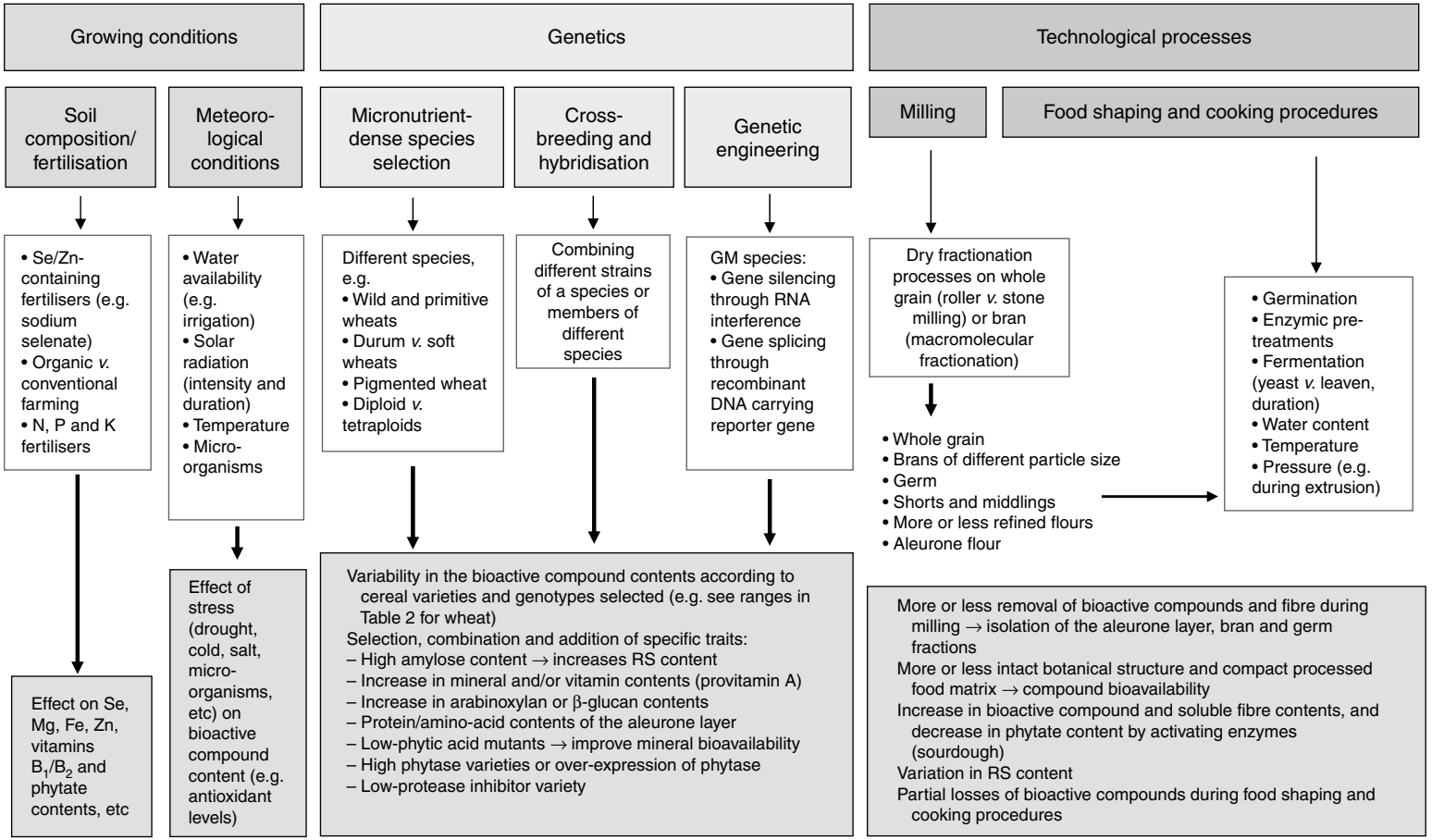

Fig. 5. Ways for improving cereal product nutritional quality. RS, resistant starch.

gene expression in relation to the nutrient synthesis and/or metabolism can be used to improve the nutritional quality of whole-grain cereals. By these means, the amylose[294,430,431], RS[416], arabinoxylan[432] and mineral/vitamin[419,433] contents can be modified (i.e. increased in most cases).

Development of new technologies. Besides growing conditions and genetics, the third way of improving the nutritional quality of cereal products is through technological processes. The literature about them is plethoric, but it is not an objective of the present paper to review them. However, some key issues may be emphasised since they allow optimising the health benefits of cereal by preserving their nutritional density and food structure.

Increasing nutritional density in bioactive compounds through germination, soaking and pre-fermentation of whole-grain cereals and/or their fractions. Cereals are usually processed in two main ways. The first is dry fractionation followed by cooking under different conditions of water content, temperature and pressure, as for pasta, biscuits, breakfast cereals and other cereal products widely consumed in Western countries. The second is fermentation. This is generally used for whole-grain cereals in more traditional procedures used for the many whole-grain foods consumed in developed countries and several alcoholic beverages (for example, beer, sake, whisky, etc) consumed around the world[434,435]. A fermentative step stimulates enzyme activities, which generally increases the content of free bioactive compounds. Bread products combine both approaches by using dry milling, fermentation and cooking.

Due to the plasma cholesterol- and glucose-lowering properties of soluble fibre and to its low content in wheat, due to the numerous health effects of free ferulic acid[261,262], and due to the relative negative effect of phytic acid upon mineral bioavailability[217], different ways to pre-hydrolyse insoluble fibre (for example, insoluble β-glucans or arabinoxylans) into soluble fibre with endohydrolases[150,436], ester-bound ferulic acid into free ferulic acid with feruloyl-esterases[437,438], and phytic acid with exogenous or endogenous phytases (i.e. through adding degrading fungal and microbial enzymes, genetic engineering to over-express phytase activity and food processes to activate endogenous phytases[217]) have been considered with the objective of increasing the bioactive potential of whole-grain cereal foods, and in the end their nutritional value.

Practically, this could be also partly achieved by using traditional and natural processes such as germination, soaking and/or fermentation in a highly hydrated medium. The fermentation of whole-grain cereals such as wheat, maize, rice, sorghum and millet, either germinated or not, often in combination with leguminous seeds (for example, soyabean and chickpea), is widespread in developed countries and the Orient for whole-grain cereal-based beverages, gruels and porridges (for example, *koko*, *doro*, *ogi*, *akasa*, *tuo zaafi* and *togwa* in Africa; *idli* in India; *shoyu* in the Orient; *chicha* in South America; or *kishk* in Arabian countries). It increases the nutritional density of the products, protects against diarrhoea, is easy to apply, allows a good preservation of the products (useful, for example, for long displacements), may improve sensory quality and is inexpensive[439–441]. Before fermentation, whole-grain cereals are generally soaked, germinated, dried and coarsely ground with a grinding stone[440]. Fermentation, by activating enzymes, can release bound bioactive compounds, synthetise new bioactive compounds, degrade anti-nutrients and increase protein and starch digestibility[439]. This is accompanied by numerous potential positive health effects as recently reviewed, for example, improved gut health or reduction of the rate of starch degradation[442]. Thus, germination and fermentation have been used for whole-grain wheat, rye, maize, sorghum and millet in order to decrease the tannin and phytic acid contents, as both compounds impair mineral bioavailability – leading to Fe-deficiency anaemia in developing countries – and also in order to increase the protein/gluten and starch digestibility and the concentration of free amino acids by enhanced proteolytic and α-amylolytic activities[177,178,180,443–449]. Sourdough pre-fermentation (incubation for 24 h at 30°C with lactic acid bacteria) for whole-wheat flour degrades about 60–70 % of the phytic acid in bread dough (compared with the initial flour content) in 4 h, so increasing Mg bioaccessibility *in vitro*[220,450] and *in vivo* in rats[451]. In another study, the type of starter for sourdough fermentation and the type of raw material (native *v.* malted or germinated rye) was shown to influence the content in bioactive compounds of the resulting wholemeal rye flour. The combination of germination and fermentation increased the levels of folates (7-fold), free phenolic acids (10-fold), total phenolic compounds (4-fold), lignans (3-fold) and alkylresorcinols, but, to a lesser extent (< 1·5-fold) the metabolic activities of microbes together with the breakdown and hydrolysis of some cereal cell walls were involved in this effect[452]. Conversely, a 4 h sourdough fermentation of whole-wheat flour leads to losses of alkylresorcinol[453]. The fermentation of rye bran also enhances the free ferulic acid and the solubilisation of pentosans through xylanase activation[454]. Recently, an increased level of free ferulic acid (about a 2-fold increase) has been reported within whole-wheat dough pizza upon 18 and 48 h of fermentation[455], as well as an increase in pentosan solubilisation and prolamin hydrolysis in germinated rye sourdough[446]. This could have practical nutritional implications as discussed earlier with free ferulic acid, and also since the soluble fraction of arabinoxylans has been shown to reduce the glycaemic response in either healthy subjects[411] or in those with impaired glucose tolerance[456]. On the other hand, prolamin proteins are known to trigger coeliac disease (autoimmune disorder due to gluten intolerance) and their intensive pre-hydrolysis during germination and fermentation might render cereal products from these technologies coeliac-safe[446]. Lastly, fermentation of whole-grain cereals has been reported in several studies to increase the content of available methionine and B vitamins, such as thiamin, riboflavin, niacin, folates and pantothenic acid, through the action of micro-organisms[439]. Despite all these convincing results, the health benefits of hydrolysis and/or the release of free bioactive compounds from whole-grain cereal products through germination and/or fermentation have not been sufficiently explored in human subjects.

The addition of a pre-fermentation step before processing other cereal products, such as those usually widely consumed in our Western societies (for example, breakfast cereals or crackers), should also be studied more. A recent study showed that adding a pre-fermentation step while omitting steam cooking before wheat flake processing preserved a satisfactorily nutritional quality by improving the management of the feeling of hunger in the morning and by moderately improving insulin economy, which could be of interest for type 2 diabetic subjects[457].

Whole-grain and wholemeal breads are generally made of flours with an extraction rate of 85–90 % (type 80 flours). Baking these flours does not sufficiently degrade phytic acid or hydrate the fibre fraction. These flours also do not generally contain the germ fraction, leading to a loss of B vitamins. One alternative would be to add 20 to 30 % whole-grain flour (with an extraction rate of 100 %) to white wheat flour[441]. The whole-grain flour could be pre-fermented in a strongly hydrated medium with leaven, and then reincorporated into white flour for baking to avoid hydration competing with gluten and fibre. This adds the germ fraction together with a significant increase in bioactive compounds while partially degrading phytic acid[441]. Sourdough whole-grain barley and wheat breads also reduce the glycaemic response in healthy subjects through delayed gastric emptying and possibly through a higher content of RS, thus prolonging satiety with potential benefits in weight control[458,459].

Reinforcing the food structure cohesiveness in processed cereal products. As preserving intact the botanical structure in whole-grain cereal products and favouring compactness of processed cereal products such as pasta reduces the glycaemic and insulinaemic responses and increases satiety, both of which are useful in the management of type 2 diabetes and weight regulation, processed cereal products with greater cohesiveness need to be identified. This can be achieved artificially by creating protein and/or fibrous networks in the food matrix to hinder enzyme accessibility to its substrate within the small intestine[460], by using intact cereal kernels with a natural fibrous network[51,54], and/or by altering kneading intensities and proving time during baking to obtain breads with a more dense crumb texture[461]. Some have also tried, with relative success, to increase the thickness of breakfast cereal flakes to reduce their glycaemic and insulinaemic indices in healthy subjects[462]. The more frequent use of more or less intact whole-grain cereal kernels in food recipes seems the most promising, easiest and cheapest way to explore by technologists.

Isolating the aleurone layer from the wheat bran fraction. Since most of the bioactive compounds are in the aleurone layer of the bran[463] and since the pericarp (especially the outer fraction composed of cellulose, penstosans and lignins is poorly digestible) may contain contaminants (pesticides, mycotoxins and heavy metals), antinutrient compounds, irritants for the digestive epithelium (for example, lignins and insoluble fibre) and may limit the bioavailability of bioactive compounds, different processes for isolating the aleurone layer from wheat bran have been investigated[464–466], with the objective of reincorporating it in cereal food recipes. This appears to be a new way of enhancing the nutrition value of cereal products[464,466]. The aleurone layer represents approximately 6–9 % of the whole-grain wheat (Fig. 1). Some researchers have studied the nutritional quality of aleurone flour, and shown that the aleurone layer is a rich source of bioavailable folate in humans[467], that it lowers plasma homocysteine[468], increases SCFA production[469], reduces colon adenoma in azoxymethane-treated rats[470], and that it is more digestible (+17 %) and fermentable (+30 %) than wheat bran, so yielding more butyrate[471]. It also has a higher antioxidant activity than wheat bran (1·5-fold) and whole-grain wheat (2-fold) *in vitro*[132,464]. However, isolating the aleurone layer from the bran fraction means losing the health benefits of lignins (mainly in the outer pericarp and testa layers of the bran fraction), which seem to be significant and remain largely unknown (see above). The long-term benefit of consuming bran and aleurone fractions on several physiological parameters and major health problems is therefore an important issue that should be explored in order to assess the real nutritional value of lignins and decide whether the few negative physiological effects generally associated with lignins are outweighed by their positive effects. The issue is close to that of phytic acid, which also has both negative and positive physiological effects. However, the issue of preserving the lignin would be the most meaningful in the case of organic whole-grain cereals which should not contain pesticides in their outer pericarp.

Conclusions

The nutritional quality of cereal products may therefore be improved by agricultural conditions, genetics and technological processes. Organic agriculture, genetics, the use of a pre-fermentation step and of a more or less intact grain structure are probably the most promising ways to preserve and enhance the nutritional density of whole-grain foods. Sourdough pre-fermentation could also be used for other whole-grain cereal foods such as breakfast cereals. The first parameter described in Fig. 5 is the milling process, and the best way to preserve a high nutritional density in bioactive compounds is to use flours with high extraction rates. It must be remembered that whole-grain wheat, wheat bran and wheat germ contain, respectively, at least 15, 52 and at least 24 % bioactive compounds and dietary fibre (Table 1). Removing the bran fraction during milling and using it to feed animals is therefore an issue to consider more seriously.

General conclusions

The importance of preserving bran and germ fractions

The bioactive compounds in whole-grain cereals are unevenly distributed (Fig. 1). Some (mainly soluble fibre, Se, some B vitamins, carotenoids and flavonoids) are present in significant quantities in the endosperm, but most are in the bran (especially the aleurone layer) and germ fractions. This fact alone shows the importance of preserving these fractions in cereal products, at least in the most currently consumed forms of breads and breakfast cereals, and to a lesser extent pasta, crackers and biscuits.

Some products consumed on special occasions (i.e. generally not at breakfast, lunch or dinner), such as cakes, pastries and viennoiseries, use very refined flours (extraction rate of 70–82 %), and it is probably not meaningful to use less refined flours. To preserve the bran and germ fractions means either reincorporating fractions later in the recipe or using the whole-grain cereal so as to maintain its botanical structure relatively intact during processing. However, reincorporation of the bran and germ fractions implies destroying the botanical structure with the loss of its health benefits (for example, increased satiety or RS content), unless technological processes can yield a cereal product with an artificial compact food structure as for pasta[472] or breads with decreased loaf volume[461].

The concept of the 'whole-grain package'

The content of individual bioactive compounds in whole grain often seems too low for them to have any significant or lasting physiological effects. It is becoming more and more evident that the synergetic action of several bioactive compounds contributes to health protection and/or the maintenance of one physiological function, not just one compound. Fig. 1 and Table 4 illustrate this concept of the 'whole-grain package': thus, obesity/body-weight regulation, CVD, type 2 diabetes, cancers, gut, mental/nervous system and skeleton health may be potentially protected by at least, respectively, ten, thirty-four, seventeen, thirty-two, ten, twenty-six and sixteen different bioactive compounds and/or groups of compounds (i.e. oligosaccharides, tocols, phenolic acids, flavonoids, saponins, inositols, γ-oryzanol, lignans and alkylresorcinols). Because of their many protective bioactive compounds (at least twenty-six), whole-grain cereals are particularly suitable for protecting the body from CVD, cancers and mental/nervous system disorders. The long-term protection against mental or nervous system disorders by consuming whole-grain cereal products therefore deserves to be studied in human subjects, notably because depression ranks among the major causes of mortality and disability with an overall prevalence of 5–8 %[274]. It is also remarkable that at least thirty compounds and/or groups of compounds may participate in antioxidant protection through different mechanisms (Tables 3 and 4), which approximately corresponds to a total of at least 3·9, 13·4 and 6·3 % of the whole-grain wheat, wheat bran and germ fractions (Tables 1 and 2). As most age-related and chronic diseases are associated with increased oxidative stress, the regular consumption of whole-grain cereal products should benefit all of us, but particularly the elderly.

The importance of pesticides and mycotoxins

Since whole-grain cereals include by definition the outer parts of the grain, they may contain pesticides and mycotoxins (for example, zearalenone and deoxynivalenol in wheat or fumonisin in maize). Their presence should not decrease the benefits of bioactive compounds also mainly contained in the outer layers. For example, there may be a relationship between the consumption of fumonisin-contaminated maize in some regions of the world (for example, China and South Africa) and the occurrence of oesophageal cancers[473,474]. However, more generally, the consequences of long-term consumption of high quantities of mycotoxin-contaminated cereal grains for human health (i.e. toxicological effects) are not well known. The link between some cancers and exposure to pesticides has been well established, particularly among farmers[475]. It is therefore particularly relevant that recommendations for the consumption of more whole-grain cereal products should be accompanied by the production of less contaminated cereals, such as those from organic agriculture devoid of pesticides.

Perspectives

It is surprising to note that, although numerous epidemiological surveys have shown a significant and positive association between whole-grain cereal consumption and the prevention of several chronic diseases, fewer studies have been performed on the mechanisms involved. For example, to my knowledge, no more than eleven studies have examined the antioxidant hypothesis by postprandial or intervention studies in human subjects to investigate the antioxidant effect of whole-grain cereals, bran or germ[136], with only a recent postprandial study on human subjects consuming wheat bran[146]. Therefore, there is a real gap between observational studies and the elucidation of the mechanisms involved. The mechanisms are certainly complex, as has been seen. But more data are needed on the mechanisms involved so as to prepare strong, convincing arguments for an increased consumption of whole-grain cereal products by the public, to better inform health professionals about their health benefits, to favour their marketing by the food industry and to develop new health claims in the near future.

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Colour versions of Figs. 1, 2 and 4 can be seen in the online version of the paper.

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Appendix 1

References cited for evaluating the range (minimum and maximum values) of bioactive compound contents in whole-grain wheat, and wheat bran and germ fractions (data for Tables 1 and 2)*

* All wheat varieties are included, i.e. durum, soft, hard, spring, winter and pigmented wheats; all data are expressed for 100 g of food. When data are expressed on a DM basis within a reference with no indication of the water content, results are converted on a fresh matter basis considering a mean water content of 13 % for whole-grain wheat, 10 % for wheat bran and 11·4 % for wheat germ (means calculated from US Department of Agriculture database for cereal grains and pasta[479]).

Whole-grain wheat

Reduced glutathione: 1·04–5·74 mg/100 g[210,480]

Oxidised glutathione: 0·86–2·88 mg/100 g[480]

Sulfur amino acids:
- Methionine: 0·17–0·24 g/100 g[479,481–483]
- Cystine: 0·19–0·40 g/100 g[479,482,483]

Sugars:
- Monosaccharides: 0·26–1·30 g/100 g[484,485]
- Sucrose: 0·60–1·39 g/100 g[482,484,485]

Total fibre (lignin, oligosaccharides, resistant starch and phytic acid included): 9·0–17·3 g/100 g[482,486–492]
- Insoluble fibre (lignin included): 9·5–11·4 g/100 g[482,488,490,493]
- Soluble fibre: 1·1–3·2 g/100 g[482,488,490,491,493]
- Cellulose: 2·1–2·8 g/100 g[479,482,494]
- Hemicellulose: 8·6 g/100 g[485]
- Lignins: 0·9–2·8 g/100 g[485–487]
- Fructans: 0·6–2·3 g/100 g[485,487,495–497]
- Raffinose: 0·13–0·59 g/100 g[482,484,485,495,496]
- Stachyose: 0·05–0·17 g/100 g[484,485]
- Total arabinoxylans: 1·2–6·8 g/100 g[482,486,487,491,498,499]
  - Water-extractable arabinoxylans: 0·2–1·2 g/100 g[486,491]
- β-Glucans: 0·2–4·7 g/100 g[485,486,491,492,498,500]
- Phytic acid: 0·28–1·50 g/100 g[482,501–506]

Fe: 1·0–14·2 mg/100 g[426,427,479,482,483,502,504,507–511]

Mg: 17–191 mg/100 g[479,482,483,504,507,511,512]

Zn: 0·8–8·9 mg/100 g[426,427,479,482,483,504,507,509,511–513]

Mn: 0·9–7·8 mg/100 g[479,482,483,504,507,509,511,512]

Cu: 0·09–1·21 mg/100 g[479,482,483,504,507,509,511–513]

Se: 0·0003–3·0000 mg/100 g[479,482,483,507,512,514,515]

P: 218–792 mg/100 g[479,482,483,507,511]

Ca: 7–70 mg/100 g[479,482,483,504,507,511]

Na: 2–16 mg/100 g[479,482,483]

K: 209–635 mg/100 g[479,482,483,504,507,511]

Thiamin (vitamin B_1): 0·13–0·99 mg/100 g[314,479,482,483,516–519]

Riboflavin (vitamin B_2): 0·04–0·31 mg/100 g[314,479,482,483,516–518]

Niacin (vitamin B_3): 1·9–11·1 mg/100 g[314,479,482,483,517,518]

Pantothenic acid (vitamin B_5): 0·72–1·99 mg/100 g[314,479,482,483,518]

Pyridoxine (vitamin B_6): 0·09–0·66 mg/100 g[314,479,482,483,516–518]

Biotin (vitamin B_8): 0·002–0·011 mg/100 g[314,482]

Folates (vitamin B_9): 0·014–0·087 mg/100 g[314,482,518,520–522]

Tocols (vitamin E) = tocopherols + tocotrienols: 2·3–7·1 mg/100 g[482,492,523–526]
- Total tocopherols: 1·06–2·89 mg/100 g[482,523–526]
  - α-Tocopherol: 0·34–3·49 mg/100 g[479,482,483,518,523–527]
- Total tocotrienols: 1·09–4·49 mg/100 g[482,523–526]

Phylloquinone (vitamin K): 0·002–0·020 mg/100 g[479,482]

Total carotenoids: 0·044–0·626 mg/100 g[479,493,528–530]

β-Carotene: 0·005–0·025 mg/100 g[479,482,527,528]

Lutein: 0·026–0·383 mg/100 g[14,527–531]

Zeaxanthin: 0·009–0·039 mg/100 g[14,527,529–531]

β-Cryptoxanthin: 1·12–13·28 μg/100 g[14]

Total phenolic acids: 16–102 mg/100 g[197,492]
- Extractable (free and conjugated) phenolic acids: 5–39 mg/100 g[197,492]
- Bound phenolic acids: 14–78 mg/100 g[197,492]
  - Total ferulic acid: 16–213 mg/100 g[197,499,527,532–535]
  - Free/soluble-conjugated ferulic acid: 0·7–4·9 mg/100 g[527,532]
  - Bound ferulic acid: 14–64 mg/100 g[197,527,532]
  - Total dehydrodiferulic acid: 1·5–76·0 mg/100 g[197,533,534]
  - Total dehydrotrimer ferulic acid: 2·6–3·5 mg/100 g[501,533]

Total flavonoids: 30–43 mg catechin equivalents/100 g[14,532]
- Free flavonoids: 2·15–4·86 mg catechin equivalents/100 g[14,532]
- Bound flavonoids: 28–40 mg catechin equivalents/100 g[14,532]
- Anthocyanins: 0·45–52·60 mg/100 g[308,493,536,537]
- Isoflavonoids:
  - Daidzein: 2·1 μg/100 g[538]
  - Genistein: 12·7 μg/100 g[538]

Lignans: 0·199–0·619 mg/100 g[293,539,540]

Alkylresorcinols: 11·6–128·8 mg/100 g[392,393,396,399,492,501,541]

Betaine: 22–291 mg/100 g[227,483,542]

Total choline: 27–195 mg/100 g[227,313,314,483,542]

Phytosterols: 57–98 mg/100 g[482,489,492,543–546]

Total D-*chiro*-inositol: 17 mg/100 g[245]

Policosanol: 0·30–5·62 mg/100 g[547]

Melatonin: 0·2–0·4 μg/100 g[308]

p-Aminobenzoic acid (PABA): 0·34–0·55 mg/100 g[313,314]

Wheat bran

α-Linolenic acid (18 : 3*n*-3): 0·16 g/100 g[548]

Reduced glutathione: about 1·7–19·4 mg/100 g[549]

Oxidised glutathione: about 6·1–21·4 mg/100 g[549]

Sulfur amino acids:
- Methionine: 0·20–0·29 g/100 g[479,482,483]
- Cystine: 0·32–0·45 g/100 g[479,482,483]

Sugars:
- Monosaccharides: 0·14–0·63 g/100 g[482,485]
- Sucrose: 1·8–3·4 g/100 g[482,485,550,551]

Total fibre (lignin, oligosaccharides, resistant starch and phytic acid included): 35·7–52·8 g/100 g[221,471,482,487–489,552–554]
- Insoluble fibre (lignin included): 32·4–41·6 g/100 g[482,485,488,493,552,555–557]
- Soluble fibre: 1·3–5·8 g/100 g[482,485,488,493,552,555]
- Cellulose: 6·5–9·9 g/100 g[471,479,482,485,556,558–561]
- Hemicellulose: 20·8–33·0 g/100 g[485,550,558–561]
- Lignins: 2·2–9 g/100 g[221,485,487,552,556,558–562]
- Fructans: 0·6–4·0 g/100 g[485,487,551]
- Raffinose: 1·08–1·32 g/100 g[482,485,550,551]
- Stachyose: 0·04–0·36 g/100 g[482,485,551]
- Total arabinoxylans: 5·0–26·9 g/100 g[471,486,487,492,554,562,563]
  - Water-extractable arabinoxylans: 0·1–1·4 g/100 g[486,492,562,563]
- β-Glucans: 1·1–2·6 g/100 g[471,485,562]
- Phytic acid: 2·3–6·0 g/100 g[471,482,505,553,556,557,559,564–566]

Fe: 2·5–19·0 mg/100 g[70,479,482,483,510,511,556,557,567]
Mg: 390–640 mg/100 g[70,479,482,483,511,559,568]
Zn: 2·5–14·1 mg/100 g[70,479,482,483,510,511,557,559,567,568]
Mn: 4–14 mg/100 g[70,479,482,483,511]
Cu: 0·84–2·20 mg/100 g[70,479,482,483,511]
Se: 2–78 μg/100 g[479,482,483]
P: 900–1500 mg/100 g[70,479,482,483,511,559,568]
Ca: 24–150 mg/100 g[70,479,482,483,511,559,568]
Na: 2–41 mg/100 g[70,479,482,483]
K: 1182–1900 mg/100 g[70,479,482,483,511]
Thiamin (vitamin B_1): 0·506–0·800 mg/100 g[314,479,482,483]
Riboflavin (vitamin B_2): 0·210–0·800 mg/100 g[314,479,482,483]
Niacin (vitamin B_3): 13·6–35·9 mg/100 g[314,479,482,483]
Pantothenic acid (vitamin B_5): 2·2–4·1 mg/100 g[314,479,482,483]
Pyridoxine (vitamin B_6): 0·704–1·303 mg/100 g[479,482,483,569]
Biotin (vitamin B_8): 0·044 mg/100 g[314,482]
Folates (vitamin B_9): 0·088–0·373 mg/100 g[314,482,521,570]

Tocols (vitamin E) = tocopherols + tocotrienols: 9·5 mg/100 g[482]
- Total tocopherols: 2·4 mg/100 g[482]
  - α-Tocopherol: 0·13–2·84 mg/100 g[479,482,483,571,572]
- Total tocotrienols: 7·1 mg/100 g[482]

Phylloquinone (vitamin K): 0·002–0·083 mg/100 g[479,482]
Total carotenoids: 0·25–1·18 mg/100 g[479,493]
β-Carotene: 0·003–0·010 mg/100 g[479,482,572]
Lutein: 0·050–0·180 mg/100 g[571,572]
Zeaxanthin: 0·025–0·219 mg/100 g[571,572]
β-Cryptoxanthin: 0·018–0·064 mg/100 g[571,572]

Total phenolic acids: 761–1384 mg/100 g[533,573]
- Extractable (free and conjugated) phenolic acids: 46–63 mg gallic acid equivalents/100 g[574,575]
- Bound phenolic acids: 148–340 mg gallic acid equivalents/100 g[574,575]
  - Total ferulic acid: 138–631 mg/100 g[154,194,263,264,365,499,533,573,575,576]
  - Free/soluble-conjugated ferulic acid: 1·34–23·05 mg/100 g[154,194,571,572,574,575,577–579]
  - Bound ferulic acid: 122–286 mg/100 g[154,574,575]
  - Total dehydrodiferulic acid: 13–230 mg/100 g[194,533,534,573]
  - Total dehydrotrimer ferulic acid: 15–25 mg/100 g[533]

Total flavonoids: 14·9–40·6 mg/100 g[193]
- Anthocyanins: 0·9–48·0 mg/100 g[493,536,537,580]
- Isoflavonoids:
  - Daidzein: 3·5 μg/100 g[293]
  - Genistein: 3·8–6·9 μg/100 g[293,538]

Lignans: 2·8–6·7 mg/100 g[221,581]
Alkylresorcinols: 215–323 mg/100 g[365,392,582]
Betaine: 230–1506 mg/100 g[227,477,483,583,584]
Total choline: 74–270 mg/100 g[227,314,477,483,583]
Phytosterols: 121–195 mg/100 g[482,543,546,585]
Total D-*chiro*-inositol: not detected[245]
Policosanol: 0·11–3·00 mg/100 g[574,586]
PABA: 1·34 mg/100 g[314]

Wheat germ

α-Linolenic acid (18 : 3*n*-3): 0·47–0·59 mg/100 g[25,548,587]
Reduced glutathione: about 19·4–245·7 mg/100 g[549]
Oxidised glutathione: about 15·3–122·4 mg/100 g[549]

Sulfur amino acids:
- Methionine: 0·39–0·58 g/100 g[479,482,483]
- Cystine: 0·35–0·61 g/100 g[479,482,483]

Sugars:
- Glucose: < 390–700 mg/100 g[482,588–590]
- Fructose: < 200–801 mg/100 g[482,588–590]
- Sucrose: 7·7–16·0 g/100 g[482,550,588–592]

Total fibre (lignins, oligosaccharides, resistant starch and phytic acid included): 10·6–24·7 g/100 g[482,487–489]
- Insoluble fibre: 8·5–18·6 g/100 g[25,482,488]
- Soluble fibre: 2·1–6·1 g/100 g[25,482,488]
- Cellulose: 7·5 g/100 g[550]
- Hemicellulose: 6·8 g/100 g[550]
- Lignins: 1·3–1·6 g/100 g[487]
- Fructans: 1·7–2·5 g/100 g[487]
- Raffinose: 5·0–10·9 g/100 g[550,588–592]
- Total arabinoxylans: 5·6–9·1 g/100 g[487,563]
  - Water-extractable arabinoxylans: 0·37 g/100 g[563]
- Phytic acid: 1·3–2·2 g/100 g[482,565,593]

Fe: 3·9–10·3 mg/100 g[479,482,483,589,594]
Mg: 200–340 mg/100 g[479,482,483,589,594]
Zn: 10–18 mg/100 g[479,482,483,589,594]
Mn: 9–18 mg/100 g[479,482,483,594]
Cu: 0·70–1·42 mg/100 g[479,482,483,589,594]
Se: 1–79 μg/100 g[479,482,483]
P: 770–1337 mg/100 g[479,482,483,589,594]
Ca: 36–84 mg/100 g[479,482,483,589,594]
Na: 2–37 mg/100 g[479,482,483,589,594]
K: 842–1300 mg/100 g[479,482,483,589,594]
Thiamin (vitamin B_1): 0·8–2·7 mg/100 g[314,479,482,483]
Riboflavin (vitamin B_2): 0·49–0·80 mg/100 g[314,479,482,483]

Niacin (vitamin B_3): 4·0–8·5 mg/100 g[314,479,482,483]
Pantothenic acid (vitamin B_5): 1–2·7 mg/100 g[314,479,482,483]
Pyridoxine (vitamin B_6): 0·49–1·98 mg/100 g[479,482,483]
Biotin (vitamin B_8): 17·0–17·4 μg/100 g[314,482]
Folates (vitamin B_9): 0·14–0·70 mg/100 g[314,482,483,521]

Tocols (vitamin E) = tocopherols + tocotrienols:
23·1–31 mg/100 g[482,524]
Total tocopherols: 21·5–30·6 mg/100 g[482,524]
α-Tocopherol: 3·1–22 mg/100 g[482,483,524,525,591]
Total tocotrienols: 1·3–1·6 mg/100 g[482,524]

Phylloquinone (vitamin K): 0·003–0·350 mg/100 g[482]
β-Carotene: 0·062 mg/100 g[482]

Extractable (free and conjugated) phenolic acids: about 51 mg/100 g[194]
Total ferulic acid: 7–124 mg/100 g[194,499]
Free/conjugated soluble ferulic acid: about 18 mg/100 g[194]
Total dehydrodiferulic acid: about 9 mg/100 g[194]

Total flavonoids: 300 mg rutin equivalents/100 g[595]
Lignans: 0·490 mg/100 g[596]
Betaine: 306–1395 mg/100 g[227,477,483]
1395 mg/100 g[477]: toasted
Total choline: 152–330 mg/100 g[227,314,483]
152 mg/100 g[477]: toasted
Phytosterols: 410–450 mg/100 g[489,546,597]
Policosanol: 1·0 mg/100 g[586]
PABA: 0·852 mg/100 g[314]

Appendix 2

References for evaluating the range of compound bioavailability and degree of fibre-type compounds fermentation from whole-grain wheat, wheat bran and/or derived products (data for Table 2).

Whole-grain wheat and derived products

Reduced glutathione: negligible in humans as free compound[209]
Stachyose and raffinose:
Completely fermented *in vitro* within 48 h as free compound[296]
97–99 % in dogs[598]

Total fibre: 34 % in human subjects fed wholemeal bread[599]
Cellulose: 20 % in human subjects fed wholemeal bread[599]
Hemicellulose: 46 % in human subjects fed wholemeal bread[599]
Lignins: 4 % in human subjects fed wholemeal bread[599]
Phytic acid: 54–79 % apparently degraded (faeces recovery) in human subjects fed Hovis bread (whole bread)[600]
Rapidly and almost fully absorbed (about 79 %) in upper part of the gastrointestinal tract of rats fed free compound[601]
Small-intestinal phytases have high activity in rats and very much lower activity in human subjects and pigs[217]

Fe: 1–20 % in human subjects fed usual diets[204]
Mg:
70 % in rats fed whole-wheat flour[219]
21–28 % in human subjects fed brown bread diet[602]
50 % in human subjects fed a typical diet[603]
57·6 % in human subjects fed a standard diet[604]

Zn:
16·6 % in human subjects consuming wholemeal bread[605]
20 % in adult women consuming whole-wheat tortillas[606]
35 % in rats fed whole-wheat flour[219]
88·9–94·6 % in rats fed whole-wheat flour[607]
18·5 % in rats fed wheatmeal[608]
60–82 % in rats fed whole-grain wheat[609]
30–37 % in rats fed whole-wheat flour chapatti[610]

Cu:
62–85 % in human subjects fed whole-wheat bread[611]
16·3–16·5 % in rats fed free compound[71,73]

Se:
81·1–84·5 % in rats fed whole-wheat flour[607]
73–86 % in rats fed whole wheat as compared with sodium selenite[612]
100 % in rats fed whole-wheat flour as compared with sodium selenite[613]
P: 41–55 % in human subjects fed brown bread diet[602]

Ca:
81·7 % in human subjects fed whole-wheat bread[614]
43–44 % in rats fed whole-wheat flour chapatti[610]
85·7–92·8 % in rats fed whole-wheat flour[607]

Thiamin (vitamin B_1): 91 % in rats fed whole-wheat bread compared with free thiamine mononitrate (100 %)[519]
Riboflavin (vitamin B_2): 95 % as oral supplement in human subjects[615]
Niacin (vitamin B_3): low[19]
Pantothenic acid (vitamin B_5): about 50 % in human subjects for average American diet[616]
Pyridoxine (vitamin B_6): 71–79 % for an average American diet compared with free compound[616]
α-Tocopherol: 70 % in human subjects fed free compound[617]
Total ferulic acid: 3·2–3·6 % urinary excretion in rats[152]
Free/soluble-conjugated ferulic acid: at least that of wheat bran in rat small intestine[154]
Bound ferulic acid: a small fraction released within small intestine by intestinal esterases[618]
Alkylresorcinols: 60–79 % from ileal samples in pigs fed whole-grain rye bread[619]
Phytosterols: weakly absorbed from the gut[620]
Total free inositols (*myo*- and *chiro*-inositol):
Apparently high in rats fed free compounds for *myo*-inositol[256]
Apparently high in women fed free compounds for *chiro*-inositol[621]
Apparently high in old human subjects fed free compounds for pinitol[622]

Wheat bran

Total fibre:
55·6 % neutral sugars in human subjects fed wheat bran[552]
34 % neutral sugars in human subjects fed wheat bran[623]
35–42 % neutral-detergent fibre in human subjects fed coarse and fine bran[561]
36·9 and 41·1 % in rats fed coarse and fine brans[624]
39 % in rats fed wheat bran[623]
49·1 % NSP in rats fed wheat bran[625]
58·8–65·0 % in pigs fed coarse and fine bran cell walls[626]
41·5 % in pigs fed wheat bran-based diet[627]

Insoluble fibre:
42·3 % in rats fed wheat bran[625]

Cellulose:
6–23 % in human subjects fed coarse and fine bran[561]
7 % in human subjects fed wheat bran[623]
13·8–21·9 % in rats fed coarse and fine brans[624]
24·1 % in pigs fed wheat bran-based diet[627]
18·2–23·7 % in pigs fed coarse and fine brans[626]

Hemicellulose:
50–54 % in human subjects fed coarse and fine brans[561]
69·4–74·4 % in pigs fed coarse and fine brans[626]
46·5 % non-cellulosic neutral sugar residues in pigs fed wheat bran-based diet[627]

Lignins:
Undigested in humans[561]
0 % in rats fed wheat bran[623]
0–4 % in rats fed processed wheat bran[628]

Soluble fibre: 72·9 % in rats fed wheat bran fibre[625]

Total arabinoxylans: 49·2 % arabinose and 71·1 % xylose in human subjects fed wheat bran[552]

Phytic acid:
Phytate from wheat bran without phytase is almost not absorbed at the intestinal level in humans[629]
58–60 % degraded into lower *myo*-inositol phosphates in ileostomates fed raw wheat bran[629,630] and only 5 % with phytase-deactivated wheat bran[629,630]
58 % degraded in ileostomates and 25 % hydrolysed for extruded wheat bran (loss of phytase activity)[630]

Fe:
3·8 % in human subjects fed rolls made of wheat bran and white wheat flour[631]
Negative effect of bran on Fe absorption is not observed in rats[632]

Se:
About 60 % in rats fed wheat bran compared with sodium selenite and selenomethionine biological value[633]
80 % in rats fed wheat bran as compared with sodium selenite[613]
P: 41–56 % in human subjects fed sodium phytate + white bread[602]
Ca: 22·3 % in human subjects fed extruded wheat bran cereals[614]

Niacin (vitamin B_3):
27–38 % in human subjects fed a concentrate of bound niacin from wheat bran[634]
17 % in rats fed a concentrate of bound niacin from wheat bran (cited in Carter & Carpenter[634])
Pyridoxine (vitamin B_6): unavailable in human subjects fed wheat bran[635]
Folates (vitamin B_9): low in human subjects fed wheat bran[467]
Tocopherols/tocotrienols (vitamin E): not available in rats fed wheat bran[636]

Bound phenolic acids:
32·7 % in pigs fed a wheat bran diet[627]
Partially and slowly solubilised from wheat bran within a human model colon[264]

Total ferulic acid:
< 5 % in small intestine of rats fed wheat bran-based diet[154]
3·9 % urinary excretion in rats fed wheat bran[152]
1·99–5·65 % urinary excretion in human subjects fed high-bran cereal[196]
Free/soluble-conjugated ferulic acid:
High in rat small intestine fed wheat bran[154]
27·77–78·92 % urinary excretion in human subjects fed high-bran cereal[196]
Bound ferulic acid: a small fraction (%?) released within rat small intestine by intestinal esterases following wheat bran consumption[618]

Dehydrodiferulic acid:
Undetectable in plasma of human subjects fed high-bran cereal[196]
Free diferulic acid can be absorbed from the gut in rats fed wheat bran[637]
Alkylresorcinols: 45–71 % from ileostomy effluents in human subjects fed rye bran soft/crisp bread[393]
Phytosterols: weakly absorbed from the gut in human subjects[620]

Appendix 3

References for the physiological mechanisms and health effects of bioactive compounds from whole-grain wheat, and wheat bran and germ fractions (data for Tables 3 and 4)*

* Keywords relative to the physiological mechanisms involved, health outcomes associated with bioactive compounds and the corresponding reference(s) are given; the models used, i.e. human, animals or *in vitro* cultured cells, may be found in references cited.

α-Linolenic acid (18 : 3*n*-3):
Health and diseases[638]; CVD[548,638–641]; anti-atherosclerotic[298]; depression and anxiety[642,643]; plasma TAG[644]; blood clotting, thrombosis, plasma lipid profile, blood pressure and inflammation[638]; colon[645] and breast[646] cancers; synthesis of cytokines and mitogens[638]; arachidonic acid (20 : 4*n*-6) and eicosanoids in tissues (such as lung) and plasma phospholipids, and

synthesis of pro-thrombotic cyclo-oxygenase-derived products (thromboxane A2 and B2, PGE2)[647]; immune system, cell signalling and gene expression[648,649]

Glutathione (reduced, GSH):

Health and diseases[650]; source of cysteine[651]; oral cancer, anti-carcinogen, antioxidant effect, binding with cellular mutagens and GSH transferase activity[110]; detoxification of toxic electrolytic metabolites, xenobiotics and reactive oxygen intermediates[652]; cellular immune function[208]

Sulfur amino acids:

Methionine:

Precursor of glutathione[200]; precursor of *S*-adenosyl methionine[653]; neural tube defects[654]; colon cancer[410]; cognitive impairment in situation of folate deficiency[653]; antioxidant activity[655]; lipotrope[239]

Cystine:

Hair and nail development[656,657]; muscle wasting[658]; antioxidant and cell signalling through reactive cysteine residues in proteins[659]

Total fibre[18,46,58,266,660,661]:

Type 2 diabetes risk[662]; risk of weight and fat gains; large bowel cancer[66,75,106,266]; satiating effect; cholesterol, bile acids, hormonal activity; immune system, toxicant transit; production of SCFA in the colon[663]; SCFA, growth of tumour cells, glutathione-*S*-transferase and genotoxic activity of 4-hydroxynonenal[664]; dilution of gut substances; energy content and glycaemic index of foods; insulin response; free radicals[93]

Insoluble fibre[63]: antioxidant-bound phenolics and colon[150]; faecal wet and dry weight and faecal bulking effect[660]; intestinal transit[660]

Soluble fibre[63]: cholesterol; glucose and insulin responses[412]; bowel health[412]

Lignins:

Antioxidant[112,149,224]; dietary carcinogens adsorption[69,266]; bile acid reabsorption[268]; bile-salt sequestrating agent[107,108]; fat absorption[665]; bile salt pool size[666]; cholesterol turnover[667]; formation of carcinogenic metabolites from bile salts[269]; precursor of lignans[221]; anti-carcinogenic[265]

Oligosaccharides (raffinose, stachyose and fructans)[295]:

Serum cholesterol[46,80]; gut modifier, enzyme modulator and binding scavenger[46]

Fructans[668,669]:

Lifespan and weight gain reduction[670]; prebiotic[18]; microbiota[671]; growth of harmful bacteria, immune system, absorption of minerals and synthesis of B vitamins[18]; absorption of Ca, Mg and Fe[18,72,73]; butyrate with cancer-preventing properties in the colon[672]; growth of cancer cells[672–674]; glycaemia and insulinaemia[668]; plasma TAG and total/LDL-cholesterol[675,676]; lipid metabolism[677]; hepatic gluconeogenesis and glycolysis[669]

Raffinose: weight gain[297]

Arabinoxylans[664]:

Colon cancer growth and progression[678]; glucose response[411]; chemoprotection and fermentation products[664]; bile acids[664]; anti-proliferative properties of butyrate[679]

β-Glucans[56]:

Satiety[54]; blood sugar and gastric emptying rate[18]; blood cholesterol[18]; hypoglycaemic and hypoinsulinaemic[680–682]; hypocholesterolaemic[56,683]; propionate, hepatocyte lipid synthesis and cholesterolaemia[684]; anti-carcinogenic[391]; immune system[391]; peripheral blood monocytes and breast cancer[685]; anti-bacterial, anti-parasitic, anti-fungal and anti-viral[391]

Phytic acid:

Risk of colon[100] and breast[101] cancers; anti-cancer agent[95,99,106,686]; antioxidant activity[148]; chelation with various metals and Fenton reaction[95]; oxidative damage to the intestinal epithelium and neighbouring cells (cited in Slavin[63]); lipid peroxidation (cited in Ferguson & Harris[69]); formation of ADP-iron-oxygen complexes that initiate lipid peroxidation[687]; cellular and nuclear signalling pathways[95]; plasma glucose (cited in Yoon *et al.*[182]); insulin and/or plasma cholesterol and TAG[688–690]; lipid levels in liver and serum[691]; detoxification capacity of liver and levels of GSH transferase and cytochrome P-450[692]; immune response[99]; renal stones[693]; calcification of cardiovascular system[694]; dental caries and platelet aggregation, treatment of hypercalciura and kidney stones, and Pb poisoning[218]; gene expression[695,696]

Resistant starch[697]:

Physically inaccessible within small intestine[18]; prebiotic[415]; glycaemic response[52]; glucose metabolism and plasma NEFA[54]; energy intake; SCFA, butyrate and colon health, and SCFA and serum cholesterol[65,80]; lipid oxidation and metabolism[67]; gallstones[698]

Fe:

Neural functioning[699]; catalase cofactor[700]; lipid peroxidation[701]; cofactor, enzymes and energy metabolism[702]; cellular energy metabolism[703]; infection and mental function[704]; cognitive development and intellectual performance[705,706]; collagen synthesis[707]; bone health[708]; aerobic endurance exercise[709]; immunity and infection[710]; vitamin metabolism[711]; serum and liver TAG, phospholipid, and cholesterol[701]; obesity[712]

Mg[204,603]:

Metalloenzymes[569]; alkaline phosphatase (bone health)[713]; antioxidant[714]; lipid peroxidation[715]; hypertriacylglycerolaemia[716] and insulin resistance[156,159,715,717,718]; diabetes[157,719–722]; glucose uptake[158], glucose metabolic clearance rate and insulin response[158,159], and oxidative glucose metabolism[723]; platelet aggregability[170]; blood pressure regulation[171]; coronary atherosclerosis and acute thrombosis[169]; vascular function[724]; blood pressure[725]; cardiovascular

death rate[726]; osteoporosis[727]; angiogenesis and inflammation[728]; stone formation[729]

Zn[204,700]:

Alkaline phosphatase cofactor; antioxidant and superoxide dismutase (SOD) cofactor[730,731]; skeletal growth and maturation, and bone metabolism[732]; chemical inactivator[46]; formation of active carcinogenic compounds[93]; Zn-binding compounds and cancer cell death[733]; oesophagus cancer[734]; Zn sensing receptor and cell signalling[735]; immune functions[736]; inflammatory diseases and cell signalling mechanisms[737]; type 2 diabetes[738]; food intake[739]

Mn[569,700]:

Antioxidant[740]; metalloenzyme constituent and enzyme activation[569]; bone health[732,741]; manganese-SOD, NF-κB activation and carcinogenic process[742]; manganese-SOD and tumour growth[743]

Cu[204,700]:

Antioxidant[744]; Cu-containing/binding proteins[569]; bone health[732,745]; central nervous system dysfunction[700]; immune and cardiac dysfunctions[700,746,747]; heart health[748,749]; anti-cancer effect and DNA binding[750]; risk of CHD[751,752]

Se[204]:

Glutathione peroxidase and thioredoxin reductase cofactor; antioxidant[46,93,753]; constituent of selenoproteins[754]; tumour growth[46,110,754,755]; prostate and colon cancer (cited in Reeves *et al.* [633]); susceptibility to carcinogens[756,757]; apoptotic effects[758]; anti-carcinogenic[759]; cell membranes and oxidation damage[760]; anti-infective[761,762]; plasma, liver and erythrocyte GSH peroxidase activity[763]; insulin resistance and vascular endothelium[764,765]; platelet aggregation[753]

P[204,603,766]:

Kidney health[766,767]; colorectal adenoma[768]; tooth development[769]

Ca[204,603]:

Colorectal cancer[770,771]; signal transduction element[772]; cell signalling[773]; mitotic events and cell cycle[774]; hypertension[603,775,776]; stroke risk[777]; diabetes risk[718]; tooth development[769]; energy balance and obesity[778,779]

Na[204]:

Fluid balance[780]; blood pressure[781]; CVD[782]; osteoporosis and bone health[783]

K[204,784,785]:

Diabetes risk[718]; insulin secretion[157,786]; blood pressure[787]; CVD[788–790]; cardiac arrhythmias[791]; kidney health[792] and stones[793]; bone health[794]; hypercalciura[795]

Thiamin (vitamin B_1)[204,796,797]:

Antioxidant[798]; glucose metabolism and Krebs cycle[799]; mental and neuronal health[800]

Riboflavin (vitamin B_2)[204,796]:

Haematopoiesis[801,802]; gastrointestinal development[803]; mental health[804]; vision[805]; cardiovascular protection[806,807]; cancer[808,809]

Niacin (vitamin B_3)[204,796]:

Hypolipidaemic and cardiovascular protection[810,811]; cancers[812]; AIDS[813]; arthritis[814]; catecholamine stimulation of lipolysis[815,816] (cited in Marcus *et al.* [817] and Figge *et al.* [810])

Pantothenic acid (vitamin B_5)[204,796]

Pyridoxine (vitamin B_6)[204,796]:

Colorectal cancer[818]; asthma and CVD[819]; impaired homocysteine metabolism and occlusive arterial disease[820]

Biotin (vitamin B_8)[204,796,821–823]:

Regulation of gene expression[824]; cell proliferation[825]; dermatological abnormalities; immune response[826,827]

Folates (vitamin B_9)[204,796,828]:

Plasma homocysteinaemia[829,830]; neural tube defects[273,831]; biochemistry of nucleic acid[828]; colon cancer risk[410,832]; anti-carcinogenic[833,834]; megaloblastic anaemia[835]; depression[274–276]; fertility[836]; lipotrope[239]; methylation and related epigenetic effects on gene expression[837]

Tocopherols and tocotrienols (vitamin E)[204]:

Cardiovascular risk[838,839]; antioxidant[840–842]; Se and reduced state (cited in Slavin[63]); formation of nitrosamines (cited in Slavin[63]); formation of carcinogens (cited in Slavin *et al.* [663]); apoptosis[843]

Tocopherols:

Non-antioxidant effects[844]; chemical inactivator (cited in Kohlmeier *et al.* [93]); protein kinase C regulation[844,845]; monocyte superoxide anion and IL-1[846]; gene expression and cell signalling[844,847,848]; peroxynitrite-derived nitrating species[849,850]; cell proliferation[851]; pancreatic carcinogenesis[852]; type 2 diabetes-induced oxidative stress[853]

Tocotrienols[347]:

Neurodegeneration and immune responses[347]; cancer[94,347,851]; cholesterol[347]; risk of heart disease; obesity and osteoporosis/bone calcification[854,855]

Phylloquinone (vitamin K)[204,700,856]:

Coenzyme and formation of γ-carboxyglutamate residues[857]; osteoporosis[858]; atherosclerosis[859]

β-Carotene:

Cancer[860]; colon cancer[106,861]; lung cancer[862–864]; tumour growth suppressor[824,865]; apoptosis[866]; immune function[867]; antioxidant[868]; coronary artery disease risk[869]

Lutein (xanthophyll family)[870,871]:

Ocular function[872]; age-related macular degeneration[873]; cataract[874]; macular pigment density[875]; antioxidant[871,876,877]; CVD, stroke and lung cancer[862,863]; skin protection[878]; colon cancer[879]; atherosclerosis[880]

Zeaxanthin (xanthophyll family):

Age-related macular degeneration[873]; cataract[881]; macular pigment density[875]; antioxidant[871,876,877]; CVD and stroke (cited in Anonymous[876]); skin protection[878]; lung cancer[862]

β-Cryptoxanthin:

Anabolic effects on bone components and bone loss/resorption[882,883]; anti-proliferative/chemopreventive agent and lung cancer[863,884–886]; carcinogenesis[887]; control of differentiation and apoptosis[888]; antioxidant (cited in Castelao & Olmedilla[889])

Phenolic acids:

Antioxidant[890]; insulin secretion[891]; plasma glucose, insulin, cholesterol and TAG (cited in Slavin *et al.*[46]); cancer and action as blocking compounds[892]; carcinogens binding to targets and release of phenolic-bound antioxidant[150,893]; tumour growth suppressor (cited in Slavin *et al.*[46] and Thompson[173]); enzyme modulators (cited in Slavin *et al.*[46]); dyslipidaemia, hepatosteatosis and oxidative stress[894]; cell signalling[186,189]

Ferulic acid[104,261,262]:

Antioxidant[895]; HDL-cholesterol[896]; hyperlipidaemia[897]; anti-carcinogenic[69], for example, tongue cancer[892]; hypotensive and vascular relaxation[898]; hypoglycaemia[899]; neurodegenerative disorders (cited in Barone *et al.*[104])

Flavonoids:

Antioxidant[69,890]; enzyme modulator, antioxidant and tumour growth suppressor (cited in Kohlmeier *et al.*[93]); anti-carcinogenic (cited in Ferguson & Harris[69] and Thompson[173]); CVD[900]; signalling molecules[188,189,191]; cell signalling, gene regulation, angiogenesis and other biological processes[214]; inflammation[189]; platelet aggregation[901]; anti-microbial[902]; production of urate[214]; bone resorption[903]; dyslipidaemia, hepatosteatosis and oxidative stress[894]

Anthocyanins:

Antioxidants[904–906]; anti-inflammatory[907,908]; anti-carcinogenic[909,910]; hypoglycaemic[911]

Isoflavonoids:

Hormone-like diphenolic phyto-oestrogens[293]; cancer and atherosclerosis[293]; osteoporosis[293]; trabecular connectivity and thickness[912]

Lignans:

Hormone-like diphenolic phyto-oestrogens[293]; antioxidant[18,45,69,96]; hormonally mediated diseases[293]; cell proliferation[97]; tumour growth suppressor[913]; precursors of enterolactone and enterodiol[96,914,915]; cancers[96]; osteoporosis[293]; rheumatoid arthritis, gastric and duodenal ulcers, skin health, diuretic, antagonistic action of platelet-activating factor receptor and action on superoxide production (cited in Thompson[173])

Alkylresorcinols[396]:

Antioxidant[916,917]; anti-carcinogenic, anti-microbial, anti-parasitic and cytotoxic, structure and metabolism of nucleic acids, phospholipid bilayer properties[400]; anti-mutagenic[918]; 3-phosphoglycerate dehydrogenase (key enzyme of TAG synthesis in adipocytes)[398]; liver cholesterol[399]

Betaine:

Fatty deposits in the liver and hyperhomocysteinaemia[919]; osmoprotectant, performance (for example, athletic)[225]; organic osmolyte[920]; CVD[921]; homocysteine and inflammatory markers related to atherosclerosis (C-reactive protein and TNF-α)[922,923]; sulfur amino acid homeostasis[924]; colorectal adenoma[121]; antioxidant and non-alcoholic fatty liver diseases[925]

Choline[226,796]:

Brain development and normal memory function[926–928]; plasma homocysteine level[929]; antioxidant[930]; carnitine conservation[931]; body fat and fatty acid oxidation[932,933]; precursor for the cell membrane phospholipids phosphatidylcholine[934], sphingomyelin[226,935], brain acetylcholine[936] and for platelet-activating-factor formation[937]; synthesis and release of acetylcholine[936,938]; lipid metabolism, hepatic secretion of VLDL, nerve function and integrity of cell membranes[226]; neural tube development[939]; lipotrope and methyl donor[240]; DNA hypomethylation and tumour development in the liver[226,239,258,940]; epigenetic regulator of gene expression[941]

Phytosterols[18,942,943]:

Total and LDL serum cholesterol[942,944–947]; micelle formation, dietary and biliary cholesterol absorption and LDL-cholesterol[948]; vascular smooth muscle cell hyperproliferation[949]; immunosuppression associated with excessive physical stress[950]; anti-inflammatory, anti-pyretic, immunomodulator and anti-diabetic (cited in Brufau *et al.*[942]); anti-diabetic and hypoglycaemic[951]

β-Sitosterol:

Growth of colon cancer line[952,953]; prostate cancer[954]; carcinogen-induced neoplasia (cited in Wattenberg[110]); apoptosis[955] through caspase activation[956]

Inositols:

Chiro-inositol:

Insulin, signal transduction and mimetic of insulin action[957]; type 2 diabetes[245,958–961]; ovulatory functions and serum androgen concentrations, blood pressure and plasma TAG[621]; folate-resistant neural tube defects[962]; pinitol and glucose metabolism[622]

Myo-inositol:

Metabolism[963]; TAG and total lipid liver, hepatic activities of glucose-6-phosphate dehydrogenase, malic enzyme, fatty acid synthetase and citrate cleavage enzyme[242,964];

conversion into *chiro*-inositol and precursor for several phospholipids (cited in Larner[957], Novak *et al.* [965] and Pak *et al.* [256]); mental health[966,967]; osmotic demyelination syndrome[968]; volume regulation during persistent osmotic stress[969]; cancer[686]; diabetic polyneuropathy and nerve conduction[970]; intestinal lipodystrophy[963]

Policosanol:

Octacosanol in human health[302]; CVD[304]; lipid, cholesterol and LDL[303,306,971–973]; cholesterol biosynthesis and LDL catabolism[973]; hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase[974]; LDL peroxidation[307]; membrane lipid peroxidation[975]; lipid metabolism[301]; platelet aggregation and thromboxane generation, endothelial damage and foam cell formation[976,977]; cytoprotection in gastric ulcer[978]; athletic performances[979]; cardiac events, and cholesterol and anti-aggregatory effects (cited in Taylor *et al.* [302]); smooth muscle cell proliferation[980]; anti-fatigue drug[302]

Melatonin[981]:

Mood, happiness, sleep and brain neuromodulation in Alzheimer's disease[309,310]; antioxidant[982,983]; corticoid receptor[984]; scavenger of hydroxyl radicals[985]; brain GSH peroxidase activity[986]; gene expression for antioxidant enzyme[987]; sleep–wake regulation[309,988]; DNA damage[989]; lifespan[990]; oncostatic role and anti-proliferative effect[311,312]; cancers[991]

para-Aminobenzoic acid (PABA):

Acetylation in blood and other tissues[315,321,992,993]; peroxisomal β-oxidation and PABA acetylation[316]; *N*-acetyltransferase regulation[994]; acetylation[319,320]; rickettsial infections and collagen diseases[995]; serum cholesterol[995]; folate formation[316]; treatment of vitiligo, leukaemia, rheumatic fever and in rickettsial diseases(cited in Barbieri *et al.* [316]); production of thromboxane[321]; anti-aggregatory[996]; UV protection of the skin (cited in Barbieri *et al.* [996] and Wang *et al.* [315]); liver folic acid metabolism (cited in Russell *et al.* [997])

γ-Oryzanol[361]:

Cholesterol and rice bran oil[998]; cholesterol absorption and aortic fatty streaks[348,358]; lipid metabolism[999]; autonomic nervous unbalance and menopausal troubles (climacteric disturbance)[999,1000]; anti-ulcerogenic[1001]; antioxidant[357,360,1002]; gene expression and oxidative stress[1003]; glycaemia control[1004,1005]; platelet aggregation[1006]; anxiety and stress ulcer[1001,1007–1009]

Avenanthramides:

Anti-inflammatory and anti-atherogenic[368]; smooth muscle cell proliferation and NO production[1010,1011]; antioxidant[140,367,369]

Saponins[370,1012,1013]:

Hypercholesterolaemia[173,374,377,1014]; lipase activity and fat absorption[1015]; transcriptional activity of Cu,Zn-SOD gene[1016]; scavenger and superoxides[1017]; hypoglycaemia[1018,1019]; gastric emptying rate and glucose transport across the brush border of the small intestine[1018,1020]; anti-fungal[374]; anti-viral[1021]; diabetes[1022]; anti-inflammatory[1019]; anti-carcinogenic[374]; tumour growth and cytostatic effect[1013,1023–1027]; bile acid binding (cited in Mimaki *et al.* [1013]); cell-mediated immune system and antibody production[375]; nervous system functioning[1012,1028]; blood coagulation[1029]